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Archives of Internal Medicine

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GEOGRAPHIC OR CLIMATIC VARIATIONS IN THE DEATH RATE FROM PERNICIOUS ANEMIA, EXOPHTHALMIC GOITER, ADDISON'S DISEASE AND ANGINA PECTORIS *

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CINCINNATI

In a preceding paper [1] it was indicated that the death rate from diabetes is apparently influenced to a marked degree by climatic conditions. The rate diminishes as one nears the equator and in general increases in the opposite directions. This was clearly shown for the states of the United States, for the countries of Europe and for Australia and New Zealand. It was suggested that this increase in the cooler, more stimulating regions probably results from an exhaustion effect of overstimulation by the highly changeable climate. To rule out the consumption of sugar as a responsible factor, the rate of the consumption of sugar was found for many countries and compared with the death rate from diabetes.[2] There was not found sufficient correlation between the two to indicate a cause and effect relationship.

It has often been suggested that overeating of other than sugar foods may be responsible for the increase in deaths from diabetes. Calculation of the consumption of food in general, however, becomes too involved to be practicable. Efforts have been directed along other lines, therefore, in an attempt to find the reason for such an alarming increase in diabetes. Other diseases of an exhaustive or overstimulative type have been studied to determine whether they exhibit similar geographic variations.

PERNICIOUS ANEMIA

Very little has been written on the geographic distribution of pernicious anemia. Bunting [3] said that there was a wide distribution, with few local variations, and that, although most reports had been of cases in the white race, the disease occurred in other races also. During a two years' stay in China, not a single case was seen or heard of by the

* Submitted for publication, April 28, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

1. Mills, C. A.: Diabetes Mellitus: Is Climate a Responsible Factor in the Etiology? **46**:569 (Oct.) 1930.

2. Mills, C. A.: Sugar Consumption in the Etiology of Diabetes Mellitus, **46**:582 (Oct.) 1930.

3. Bunting, C. H.: Bull. Johns Hopkins Hosp. **16**:222, 1925.

writer. No cases among the Chinese have been reported in the medical literature. It is likewise rare among the Japanese according to information obtained in conversation with Japanese physicians. Unfortunately, the Japanese death statistics do not list pernicious anemia as a separate cause of death.

In table 1 is given the death rate from pernicious anemia in the states of the registration area of the United States. The data leave no doubt that there is a low death rate in the southern states, the mean for eleven states being 2.1 per hundred thousand of population. Next comes the mountain and plateau states with 4, and finally the central

TABLE 1.—*Deaths from Pernicious Anemia per 100,000 Estimated Population in the States of the Registration Area*

(Mean for the years 1921 to 1926)

Southern States		Central and Northern States	
Florida	3.8	Maine	7.7
South Carolina	1.2	Vermont	9.2
Georgia	1.4	New Hampshire	9.4
Alabama	1.2	Massachusetts	7.4
Mississippi	1.0	Connecticut	5.3
Louisiana	1.7	Rhode Island	6.0
North Carolina	1.7	New York	5.5
Virginia	2.2	Michigan	9.7
Tennessee	2.8	Wisconsin	9.0
Kentucky	2.8	Minnesota	9.7
West Virginia	3.5	North Dakota	5.6
Mean for 11 states	2.1	Washington	6.3
Western Plateau States		Oregon	6.7
Arizona	2.7	California	7.4
Utah	5.0	Kansas	6.9
Colorado	6.0	Nebraska	6.9
Wyoming	2.8	Iowa	10.4
Idaho	3.0	Missouri	4.7
Montana	4.3	Illinois	6.2
Mean for 6 states	4.0	Indiana	6.4
		Ohio	6.0
		Pennsylvania	4.7
		New Jersey	4.4
		Maryland	3.7
		Delaware	3.8
		Mean for 25 states	6.8

and northern states with rates ranging up to 10.4, the mean being 6.8 per hundred thousand of population. The low incidence among Negroes would account for a part of the low death rate of the southern states, but if the total deaths from pernicious anemia were calculated only on the white population, the rate would still be less than half that found in the northern states. It is to be noted that the states of the upper Mississippi and Missouri river valleys and of northern New England, where the stimulating extremes of climate are most often encountered, are the places of highest incidence. Florida and Colorado show high rates for their locations, probably because of migration of the more well-to-do people from states with higher rates.

Table 2 sets forth similar data for other countries. In this table an arbitrary division is made, one group containing all countries with a

rate greater than 3 per hundred thousand of population and the other group, countries below this level. A comparison of this table with a similar table for the death rate from diabetes shows a striking likeness. The same countries that have such a high, and increasing, death rate from diabetes are also the ones similarly afflicted with pernicious anemia, while near the equator both disease are much less fatal. This difference cannot be racial, for in the countries with low rates there are Italy, Uruguay and Iceland mainly populated by the white race, Ceylon by Indians, the Philippines and the Straits Settlements by the yellow and brown races and Nigeria and Haiti by the black.

TABLE 2.—*Pernicious Anemia Death Rates in Various Countries*

Country	Year	Deaths per One Hundred Thousand Population from Pernicious Anemia	Deaths from Pernicious Anemia as Percentage of Total Deaths
Northern Ireland	1927	10.7	0.73
Scotland	1926	10.6	0.86
Canada	1926	9.3	0.81
Irish Free State	1927	7.4	0.50
England and Wales	1927	6.8	0.55
United States	1926	5.7	0.46
Norway	1926	5.4	0.50
Netherlands	1927	4.4	0.43
New Zealand	1928	3.8	0.45
South Africa	1926	3.1	0.32
Italy	1925	2.3	0.14
Uruguay	1927	2.2	0.19
Barbados	1927	2.0	0.10
Nigeria	1927	2.0	0.10
Philippine Islands	1925	1.8	0.10
Straits Settlement	1927	1.5	0.05
Hawaii	1927–8	1.5	0.13
Iceland	1911–15	1.2	0.09
Haiti	1927	0.3	0.06
Ceylon	1928	0.3	0.01

There would, therefore seem to be a definite geographic, or climatic, distribution of deaths from this cause. Iceland forms one exception here, as it did for diabetes. Although Japan and northern China should fall, geographically, into the upper half of table 2 in regard to their distance from the equator, their actual death rate from pernicious anemia must be fully as low as in the tropical countries. Whether this is due to racial influence or to the severe tropical summer which they must endure, can only be conjectured.

In the countries with high death rates from pernicious anemia, the rates were rising rapidly up to 1926, but in almost all these same countries there has been a marked fall since that year. This probably results from the relief afforded by liver diets and liver extracts during this recent period.

EXOPHTHALMIC GOITER

Since this disease probably most nearly represents the effects of individual metabolic overstimulation, it was deemed advisable to include it in the statistical study. There has been much speculation as to the basis of this overstimulation, but no definite proof has been advanced. Climate has not been considered as an important etiologic factor.

In table 3 is presented the death rate by states in the United States for the year 1927. Not only is there an exceedingly low death rate from this cause in the southern states (1.5) as compared with the north (4), but among the southern states it is seen that the rate rises with the pro-

TABLE 3.—*Deaths from Exophthalmic Goiter per 100,000 Estimated Population in the States of the Registration Area for 1927*

Southern States		Central and Northern States	
Florida	1.3	Maine	1.4
South Carolina	0.8	Vermont	4.0
Georgia (1928)	0.9	New Hampshire	1.1
Alabama	1.1	Massachusetts	1.3
Mississippi	0.8	Connecticut	1.5
Louisiana	1.2	Rhode Island	1.9
Arkansas	0.7	New York	2.7
North Carolina	1.1	Michigan	7.5
Arizona	1.5	Wisconsin	8.0
Tennessee	1.6	Minnesota	5.7
Kentucky	2.3	North Dakota	3.1
Virginia	2.7	Washington	5.8
West Virginia	3.5	Oregon	7.1
		California	2.8
Mean for 13 states	1.5	Kansas	5.3
		Nebraska	4.4
Western Plateau States		Iowa	4.5
		Missouri	5.0
Utah	4.2	Illinois	7.1
Colorado	4.7	Indiana	7.8
Wyoming	1.3	Ohio	7.0
Idaho	4.0	Pennsylvania	3.8
Montana	3.4	New Jersey	1.8
		Maryland	3.4
Mean for 5 states	3.5	Delaware	1.6
		Mean for 25 states	4.02

gression from south to north. Florida provides the exception here as in the case of pernicious anemia and diabetes mellitus, and probably for similar reasons; i. e., there is a migration on a large scale from northern states where the rates are higher.

It is interesting to note the low rate in all states having comparatively extensive contact with the Atlantic ocean, even up to, and including, Maine, while the Pacific coast states show high rates. No explanation can be offered for this observation at present. One might be tempted to attribute the low rate in the coastal states of the south to the same cause, but in this region the inland states also show comparatively low rates. The north central states that have such a high prevalence of simple goiter also have the highest death rates from exophthalmic goiter.

It is of interest in this connection to compare the death rates from this cause in the provinces of Canada:

	Deaths from Exophthalmic Goiter per 100,000 Population, 1926		*Deaths from Exophthalmic Goiter per 100,000 Population, 1926*
Canada	3.5	Ontario	6.3
Prince Edward Island	0.0	Manitoba	3.6
Nova Scotia	0.9	Saskatchewan	2.4
New Brunswick	1.0	Alberta	2.1
Quebec	1.6	British Columbia	4.4

Here again is seen a very low rate in the Atlantic coast provinces, a very high rate in the region of the Great Lakes, a medium rate in the

TABLE 4.—*Death Rates from Exophthalmic Goiter in Various Countries*

Country	Year	Deaths from Exophthalmic Goiter Per One Hundred Thousand Population
Jamaica	1927	4.2
United States	1927	4.0
New Zealand	1928	3.7
Canada	1926	3.5
England and Wales	1928	2.7
North Ireland	1928	2.4
Straits Settlements	1927	2.0
Scotland	1928	1.9
Irish Free State	1927	1.7
South Africa	1926	1.3
Holland	1928	1.1
Switzerland	1925	1.0
Japan	1918	0.56
Norway	1926	0.4
Italy	1925	0.4
Uruguay	1927	0.35
Hawaii	1927–8	0.3
Philippine Islands	1925	0.17
Spain	1926	0.17
Haiti	1927	0.05
Ceylon	1928	0.04
Colombia	1927	0.04
Grenada	1927	0.00
British Guiana	1927	0.00
Barbados	1927	0.00

prairie provinces and a high rate again along the Pacific coast. This very low rate along the Atlantic coast in the United States and Canada and the high rate along the Pacific coast deserve further study. McClendon [4] has attempted to correlate the incidence of exophthalmic goiter with low iodine values in surface and drinking waters, but his data are not entirely convincing. It is hoped that this question may be taken up in a future article.

In table 4 the death rate from exophthalmic goiter is given by countries, arranged in a descending order of death rate values. An arbitrary division is made, with those countries having a rate of 1 or more per hundred thousand of population in one group and those with a rate below 1 in the second group. With the exception of Jamaica and the

4. McClendon, J. F.: Inverse Relation Between Iodin in Food and Drink and Goiter, Simple and Exophthalmic, J. A. M. A. **82**:1668 (May 24) 1924.

Straits Settlements in the first group and of Norway in the second group, the same distribution of the death rates was found as that for diabetes and pernicious anemia. The countries farther from the equator have the higher rates, while the warmer countries have the lower rates. Japan, although placed well northward, falls into the tropical group. Personal observation in North China indicated a similar low incidence of exophthalmic goiter there. It is probably more than a coincidence that the orient should be so similar to the tropics in the low death rates for these diseases.

TABLE 5.—*Deaths from Addison's Disease and Tuberculosis (All Forms) per 100,000 Population in the States of the Registration Area*

Southern States	Addison's Disease 1927	Tuberculosis (All Forms) Mean for 1920, 1925, 1926
Florida	0.07	91.7
South Carolina	0.06	101.6
Georgia	0.05	.....
Alabama	0.1	97.1
Mississippi	0.06	115.0
Louisiana	0.06	119.1
Arkansas	0.2	.....
North Carolina	0.1	104.6
Arizona	0.2	328.5
Tennessee	0.2	150.0
Kentucky	0.2	131.6
Virginia	0.1	119.1
West Virginia	0.1	76.7
Mean for 13 states..	0.1	
Western Plateau States		
Utah	1.0	34.1
Colorado	0.6	174.0
Wyoming	0.0	28.6
Idaho	0.2	34.2
Montana	0.6	62.7
Mean for 5 states...	0.5	

Central and Northern States	Addison's Disease 1927	Tuberculosis (All Forms) Mean for 1920, 1925, 1926
Maine	0.3	79.3
Vermont	0.0	77.7
New Hampshire	0.7	77.7
Massachusetts	0.3	90.1
Connecticut	0.3	89.8
Rhode Island	2.9	95.4
New York	0.4	100.9
Michigan	0.4	73.2
Wisconsin	0.4	70.8
Minnesota	0.6	70.9
North Dakota	0.9	47.8
Washington	0.3	83.6
Oregon	0.3	71.9
California	0.5	145.5
Kansas	0.2	44.5
Nebraska	0.4	35.9
Iowa	0.4	40.0
Missouri	0.5	92.7
Illinois	0.3	85.0
Indiana	0.4	91.4
Ohio	0.5	83.7
Pennsylvania	0.3	86.3
New Jersey	0.3	92.7
Maryland	0.2	127.1
Delaware	0.4	118.5
Mean for 25 states...	0.5	

Jamaica and the Straits Settlements, the two tropical regions that have the higher exophthalmic goiter rates, have both developed this high rate within the last three or four years. Previous to that time there were no deaths from these diseases in most years, with a very low average rate. It would indeed be of great interest to find what economic or health changes have taken place recently in these localities.

ADDISON'S DISEASE

Tuberculosis of the suprarenal glands is the most frequent pathologic observation following death from Addison's disease, and yet if mortality statistics for this disease are at all reliable, its incidence does not correspond even remotely to the incidence of tuberculosis. The death rates, by states, for these two diseases are shown in table 5. Table

10 gives a comparison of the various rates for white and colored population in the states that classify their deaths in this way. In this table it is seen that although the death rate from tuberculosis in the colored population is about three times as high as that in the white, Addison's disease is rare. It seems unlikely, therefore, that the clinical diagnosis of Addison's disease, on which most death certificates are based, bears any direct relationship to the incidence of tuberculosis among the population. A similar comparison of data based on diagnoses at autopsy would be more valuable. An effort will be made to get such a comparison.

TABLE 6.—*Death Rate from Addison's Disease in Various Countries*

Country	Year	Deaths per One Hundred Thousand Population per Year
Jamaica	1927–8	0.7
New Zealand	1921–3	0.6
England and Wales	1915–28	0.6
Scotland	1923–8	0.6
Canada	1921–6	0.5
Australia	1921–7	0.5
North Ireland	1927–8	0.5
Irish Free State	1927–8	0.5
Switzerland	1911–20	0.5
Argentina	1913	0.2
Prov. of Tucuman	1924	0.5
Prov. of Buenos Aires	1924	0.4
Norway	1922–6	0.4
United States	1922	0.3
Union of South Africa	1922–6	0.3
Netherlands	1922–8	0.3
Hawaii	1927–8	0.3
Iceland	1911–15	0.2
Costa Rica	1927	0.2
Uruguay	1927	0.18
Cuba	1921–5	0.09
Ceylon	1928	0.04
Japan	1918	0.04
Philippine Islands	1925	0.01
Barbados	1927–8	0.00
Straits Settlements	1924–8	0.00
Granada	1923–8	0.00
Nigeria	1926–7	0.00

The very low mean rate, 0.1 per hundred thousand of population, from Addison's disease in the southern states, and the mean rate of 0.5 in the northern states is difficult to explain except on a climatic basis. The more intense industrialization in the north cannot be blamed, for the highest rates are found in the states with predominantly rural population. Neither can the rarity of the disease in the Negro be the reason for the low southern rate, for table 10 shows the rate for the southern white population to be far below that of the north. It would seem, then, most likely that the greater climatic stimulation of the northern states is responsible for the deaths from suprarenal failure. Table 6, presenting the death rates from Addison's disease over the world, shows the same climatic variations as were noted for the other metabolic diseases and for this disease in the United States.

ANGINA PECTORIS

During almost two years of hospital experience in China the author saw little advanced arteriosclerosis or its complications in the Chinese people. Blood pressure in the Chinese ranges considerably below the levels common in northern United States, and the basal metabolism and general scale of physical activity are correspondingly low. Since a high metabolic drive may perhaps be the causative force in a great portion of the cases of arteriosclerosis seen today, it was deemed advisable to get mortality statistics on this point if possible. Angina pectoris was considered as probably the best index to vascular change that would

TABLE 7.—*Deaths from Angina Pectoris per 100,000 Population in the States of the Registration Area for 1927*

Southern States		Central and Northern States	
Florida	16.0	Maine	39.6
South Carolina	11.7	Vermont	33.4
Georgia	9.4	New Hampshire	47.0
Alabama	6.7	Massachusetts	22.4
Mississippi	7.1	Connecticut	18.0
Louisiana	12.8	Rhode Island	17.9
Arkansas	4.7	New York	19.6
North Carolina	9.5	Michigan	14.1
Arizona	9.4	Wisconsin	11.7
Tennessee	9.7	Minnesota	10.8
Kentucky	10.0	North Dakota	9.0
Virginia	13.6	Washington	17.4
West Virginia	7.5	Oregon	18.2
		California	23.7
Mean for 13 states	9.2	Kansas	13.1
		Nebraska	12.7
Western Plateau States		Iowa	16.7
Utah	10.2	Missouri	11.0
Colorado	15.6	Illinois	12.3
Wyoming	6.6	Indiana	18.8
Idaho	9.4	Ohio	14.7
Montana	8.8	Pennsylvania	12.5
		New Jersey	16.7
Mean for 5 states	10.1	Maryland	19.2
		Delaware	15.2
		Mean for 25 states	18.6

appear in mortality statistics. The certainty of diagnosis in this disease should not differ greatly in different countries, so that valuable comparison should be obtained.

In table 7 is shown the death rate from angina pectoris in the various states for 1927. The rate in the southern group of states is seen to be just about half that of the northern states. The rate in Negroes is lower than that in the white population in the south, but the rate in the white population in the south is only about two-thirds as high as that in the north (see table for white and Negro rates). Table 8 gives a similar comparison by countries. Here the same climatic differences in the death rate are noted as those found for the diseases previously considered. This is the more interesting in that this disease can scarcely be considered in any way as a direct metabolic disturbance; and still it shows the same world variations in death rate as were manifest for diabetes, exophthalmic goiter, etc.

ACUTE INFECTIOUS DISEASES

In considering the data presented for the metabolic diseases and angina pectoris, many will say that the differences in death rates from these diseases may be explained on the basis of a wide difference in the incidence of the acute infectious diseases. It is a common belief that their incidence is much higher in the northern countries and states, and that they act to bring on the metabolic diseases. In order to show that this difference is not sufficient to serve as an important factor in determining the death rates for the metabolic diseases and angina pectoris, table 9 is presented. Only the mean death rates by groups of states are

TABLE 8.—*Deaths from Angina Pectoris per 100,000 Population in Various Countries*

Country	Mean Rate	Period of Years	Recent Rate	Year
Switzerland	....	.....	16.0	1925
United States	....	.....	14.7	1927
Canada	10.6	1923–6	12.3	1926
Scotland	8.7	1923–8	11.7	1928
Jamaica	8.9	1923–6	10.5	1927
New Zealand	7.4	1924–8	9.4	1928
England and Wales	6.0	1924–8	9.4	1928
Cuba	8.8	1922–5	8.9	1925
Spain	8.1	1923–6	8.0	1926
Australia	6.3	1924–7	7.8	1927
Chile	6.7	1927–8	7.2	1928
Union of South Africa	6.7	1923–6	6.8	1926
Hawaii	6.2	1927–8	....	....
North Ireland	4.2	1924–8	5.7	1928
Holland	4.8	1924–8	4.3	1928
Uruguay	....	.....	4.8	1927
Italy	4.4	1924–5	4.4	1925
Colombia	....	.....	4.4	1927
Irish Free State	2.8	1925–7	3.3	1927
Barbados	1.8	1925–7	3.0	1927
Grenada	1.7	1923–8	0.0	1928
Costa Rica	....	.....	1.5	1927
Philippine Islands	....	.....	1.4	1925
Panama	0.5	1923–6	1.1	1926
Ceylon	....	.....	0.5	1928
Straits Settlements	0.5	1924–8	0.8	1928
British Guiana	0.4	1924–8	0.3	1928
Haiti	0.3	1926–7	0.3	1927
Nigeria	0.0	1926–7	....	....

given here. Pneumonia (all forms), acute and chronic nephritis and acute rheumatic fever were taken as representative acute infectious diseases. From the table it is seen that no significant difference in the death rates from these diseases exists in the different regions of the United States.

COMPARISON OF THE DEATH RATES FOR THE WHITE AND THE COLORED POPULATIONS

In table 10 it is seen that the death rate for pernicious anemia, etc., is lower in the Negro than in the white population, but with the acute infectious diseases and tuberculosis, the reverse is the case. This fact is strong evidence against the theory that acute infections are major

basic factors in determining the prevalence of the diseases considered. In the case of Addison's disease the lack of association with tuberculosis is strikingly brought out. The Negroes have practically no deaths from Addison's disease, although the death rate from tuberculosis is roughly three times as high as that of the white population, and shows

TABLE 9.—*Deaths from Certain Acute Infectious Diseases per 100,000 Estimated Population in the States of the Registration Area*

	Pneumonia (All Forms) 1926	Acute and Chronic Nephritis 1926	Acute Rheumatic Fever 1927
Mean for 11 southern states	80.1	84.0	1.8
Mean for 5 western plateau states	74.1	53.8	2.9
Mean for 25 central and northern states	98.3	97.5	2.3

TABLE 10.—*Deaths from the Various Diseases Considered, per 100,000 Estimated "White" and "Colored" Population (1927)*

	Pernicious Anemia		Exophthalmic Goiter		Addison's Disease		Angina Pectoris	
State	White	Colored	White	Colored	White	Colored	White	Colored
Florida	3.0	2.3	1.6	0.5	0.1	0.0	19.3	8.6
Alabama	1.8	0.8	1.0	1.3	0.12	0.11	8.8	2.8
Mississippi	0.9	0.5	1.1	0.6	0.1	0.0	11.6	3.0
Georgia (1928)	1.1	1.2	1.2	0.4	0.1	0.0	11.5	6.0
Louisiana	1.7	0.15	1.1	1.5	0.08	0.0	13.4	12.0
Arkansas	1.0	1.4	0.6	0.8	0.3	0.0	5.9	2.4
South Carolina	1.9	1.1	1.2	0.3	0.1	0.0	15.4	7.7
North Carolina	2.4	1.2	1.3	0.7	0.15	0.0	11.0	5.7
Tennessee	2.7	1.2	1.5	2.1	0.2	0.0	11.0	3.7
Virginia	2.5	1.5	2.7	2.5	0.2	0.0	14.7	10.8
Kentucky	3.2	1.4	2.1	4.7	0.13	0.5	9.2	19.4
Maryland	2.0	0.4	3.7	2.0	0.2	0.0	21.3	8.2
Missouri	4.4	0.0	4.7	2.5	0.24	0.0	19.9	9.1

	Acute Rheumatic Fever		Tuberculosis (All Forms) 1926		Acute and Chronic Nephritis 1926		Pneumonia (All Forms) 1926	
State	White	Colored	White	Colored	White	Colored	White	Colored
Florida	2.0	3.0	57.9	162.6	119.4	146.3	68.9	125.2
Alabama	1.7	2.6	52.6	170.1	72.8	109.1	77.6	129.8
Mississippi	0.9	2.2	50.7	163.1	96.7	124.4	79.2	105.9
Georgia (1928)	.....	.....	.....	.....	.....	.....	.....	.....
Louisiana	1.0	3.0	59.7	185.5	91.0	146.0	74.2	140.8
Arkansas	1.1	2.5	.....	.....	.....	.....	.....	.....
South Carolina	2.1	3.0	42.5	142.1	101.6	138.0	72.4	104.5
North Carolina	2.4	3.2	64.1	179.4	88.8	129.8	78.0	131.6
Tennessee	2.0	4.0	111.0	320.7	67.1	138.5	89.7	183.9
Virginia	2.1	4.9	71.5	191.9	97.3	149.8	68.6	133.6
Kentucky	2.7	12.8	106.2	299.7	78.7	212.7	85.8	200.6
Maryland	2.3	11.7	86.3	257.6	143.5	227.1	121.4	284.3
Missouri	1.3	5.1	.....	.....	.....	.....	.....	.....

a great increase toward the north. This increase in rate toward the north is shown for both the white and colored population of the south for most of the metabolic diseases.

COMMENT

No doubt various objections will be raised against interpretations based on the death statistics presented here. Foremost among these objections will be the argument that the low rates for these metabolic

diseases in our southern states may well be caused by laxity or errors of diagnosis on the part of the medical profession in this area. There is no direct proof that such is not the case. However, the European data supply valuable evidence that the differences in death rates north and south are real and not faults in diagnosis, for surely Italy, with metabolic disease death rates similar to those of our southern states, compares favorably with the countries of northern Europe in the diagnostic ability of its medical profession.

The lower death rate for the metabolic diseases in rural districts may suggest to some the likelihood of laxity of medical diagnosis in the country districts, but in England and Wales the country rates are higher than the urban rates. Although the fact is recognized that crude death rates can be no more reliable in general than are the death certificates sent in by the physicians, I see no valid objection to their use for comparative purposes in different areas. Perhaps the greatest factor of error which should be kept in mind is the difference in the distribution in age and life expectancy of the population in different countries. Diabetes and angina pectoris are diseases of the more advanced ages, and would therefore be less prevalent in countries having a shortened mean life span. However, exophthalmic goiter and Addison's disease show their maximum death rate at considerable earlier ages, so that this factor of shortened life expectancy would influence them much less; and still they show the same geographic differences as do diabetes, pernicious anemia and angina pectoris. Mathematical treatment of the problem may well show the exact importance of the climatic factor.

From the data presented there is a strong suggestion of climatic suppression of the metabolic diseases in those tropical and subtropical areas where other metabolic functions are also lowered by the heat. The consumption of oxygen, the blood pressure and the expenditure of energy in general are lowered, resulting in a lessening of the metabolic strain, so that the exhaustive or overstimulative diseases of metabolism appear with less frequency. It is of especial interest that Japan and northern China are found to be similar to the tropics in this characteristic. Although their winter is severe and stimulating, it cannot be sufficient to counterbalance the severe depressive influence of the prolonged moist heat of their tropical summer.

The part played by differences in diet is impossible of evaluation at present. It is significant, however, to note that Americans going to China and continuing on practically unchanged dietary standards, show a distinct fall in blood pressure within two years, while Chinese coming to America show a rise. Attempts are in progress to correlate climatic differences with differences in as many phases of body metabolism as possible. The next article will deal with the relation of climate to conception rates.

DIABETES MELLITUS

THE COLLOIDAL OSMOTIC PRESSURE OF THE BLOOD *

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The primary purpose of this investigation was to attempt to find the cause of wide discrepancies met with occasionally between the cholesterol content of the blood and the clinical picture in diabetes mellitus. Theoretical considerations led to a physicochemical study of the blood of such patients. The results obtained appear to be not only of clinical, but of biologic, interest in general.

Determination of the cholesterol content of blood plasma has been a routine procedure in the diabetic clinic of the Montreal General Hospital for a number of years.[1] As with all other laboratory tests, with the accumulation of data and their correlation with the clinical states, anomalous results are met with that cannot be accounted for by technical error. For example, high cholesterol values may be found in the absence of conditions with which they are usually associated in diabetes (severe diabetes, acidosis, ingestion of food of high sterol content, pregnancy, infections, nephritis, disease of the biliary passages, etc.). In searching the literature for a possible explanation of these unexpectedly high values, attention was drawn to a recent observation by Fishberg.[2] This author demonstrated an intimate relationship between the colloidal osmotic pressure of blood and its lipoid content.

It has been known for some time that lipemia may result from, or be associated with, lowering of the concentration of blood proteins. Striking clinical examples are chronic nephritis with edema, so-called nephrosis and hemorrhage. All of these conditions have one feature in common, namely, anemia, and lipemia has been attributed to the latter by lowering oxidation or loss of blood lipase. In a discussion of this phase of the subject, however, Fishberg aptly pointed out that, though loss of red blood cells may be a contributing factor in the production of lipemia, it cannot be the only or the most important one, since in pernicious anemia—a condition exhibiting at times most severe grades of anemia—lipemia is the exception rather than the rule. As a matter of fact, one

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1. Rabinowitch, I. M.: Canad. M. A. J. **17**:171, 1927.
2. Fishberg, E. H.: J. Biol. Chem. **81**:205, 1929.

of the characteristics of this disease is that fat depots are well filled. On the basis of bleeding experiments in animals, Fishberg concluded that the important factor in the production of lipemia in the aforementioned conditions is loss of blood proteins, and suggested that the lipoids are mobilized in an effort to compensate for the decreasing osmotic pressure exerted by the proteins.

A not uncommon association with the aforementioned high cholesterol values is edema. The latter may manifest itself clinically in four ways: (*a*) puffiness of the eyelids, (*b*) pitting of the skin on pressure, (*c*) no obvious edema but rapid gain of body weight out of all proportion to food (caloric) intake or (*d*) a stationary body weight in spite of a diet of low caloric content.[3] Among diabetic patients who are not taking insulin, the commonest cause of edema (excluding heart and kidney disease) is ingestion of large quantities of salt, either as table salt or in foods of high salt content. In diabetic patients treated with insulin, there may be an additional factor, namely, "insulin edema."[4] In connection with these observations, it is interesting here to note that Boyd,[5] in a study of the blood cholesterol in juvenile diabetes, found that high values for blood cholesterol were usually associated with cases of hydremia. No data with regard to the protein contents of the bloods in these cases are recorded.

In view of these observations, the possibility that high values for cholesterol may at times be a compensatory phenomenon resulting from dilution of blood has to be considered. Simple estimation of total protein would appear sufficient to test this possibility. A complicating factor, however, is the fact that the colloidal osmotic pressure of the blood appears to depend not only on the total protein content, but also on (*a*) the relative proportions of the different forms of protein (albumin, globulin and fibrinogen) and (*b*) the degree of dilution of the blood. A brief observation with regard to the last named phenomenon is necessary since the standards employed in this investigation were dependent on it.

Starling[6] first demonstrated that serum protein exerts an osmotic pressure. In 1926, working independently, Mayrs[7] and Verney[8] showed that when a sample of plasma was diluted with Ringer's solution, the observed fall of colloidal osmotic pressure was greater than could be

3. With regard to conditions (*c*) and (*d*), the term edema merely implies retention of water; the fluid may be within the cells or extracellular.

4. Rabinowitch, I. M.: Canad. M. A. J. **17**:685, 1927.

5. Boyd, Gladys L.: Blood Cholesterol in Diabetic Children, Am. J. Dis. Child. **38**:490 (Sept.) 1929.

6. Starling, E. H.: J. Physiol. **19**:312, 1896.

7. Mayrs, E. B.: Quart. J. Med. **19**:273, 1925-1926.

8. Verney, E. B.: J. Physiol. **61**:319, 1926.

attributed to the proportional decrease of protein. More recently, Fishberg [2] made similar observations. The effect of dilution on colloidal osmotic pressure is shown in table 1 and graphically recorded in charts 1 and 2. In their original forms, the values were expressed differently by the various authors; the protein concentrations were recorded in terms of protein and protein nitrogen, and the osmotic pressure was expressed in terms of centimeters or millimeters and as serum and water. The data were, therefore, recalculated in terms of millimeters and as total osmotic pressure and osmotic pressure per gram of protein. It will be noted that

TABLE 1.—*Effects of Dilution of Blood on Osmotic Pressure*

Verney			Mayrs			Fishberg		
Protein, per Cent	Osmotic Total	Pressure* per Gm. Protein	Protein, per Cent	Osmotic Total	Pressure per Gm. Protein	Protein, per Cent	Osmotic Total	Pressure† per Gm. Protein
9.37	498	53	7.87#	402	51	7.21	353	49
7.00	336	48	7.09	348	49	6.39	301	47
6.56	324	49	6.30	290	46	5.77	283	48
6.37	295	46	5.51	247	45	5.05	219	43
6.31	282	45	4.72	202	43	4.32	169	39
6.25	275	44	3.93	157	40	3.61	106	29
6.19	292	47	3.15	118	37	2.80	75	26
5.57	200	36	2.36	78	33	2.16	29	13
4.60	171	37	1.57	48	31			
4.50	158	35	0.79	24	35			
4.37	149	34	8.12§	401	49			
4.19	136	32	5.69	229	40			
3.87	129	33	4.06	146	36			
3.81	133	35	3.25	112	34			
3.56	117	33	2.44	81	33			
3.44	115	33	1.62	50	31			
3.34	108	32	0.81	24	30			
3.12	74	24						
2.75	66	24						

* Mm. water.
† Mm. serum or plasma.
\# Mixed blood (normal).
§ Individual blood (normal).

as the dilution increases, not only does the total colloidal osmotic pressure fall, but the pressure per gram of protein also decreases.

Explanation of the decrease of colloidal osmotic pressure with alteration of the relative proportions of the different forms of protein appears simple. Since osmotic pressure depends on the number of particles, and since both the particles of fibrinogen and globulin are larger than those of albumin, with preponderance of the former in a given amount of protein solution, one would expect a fewer number of molecules in a given volume and therefore a lower pressure per gram of protein. Explanation of the decrease of pressure per gram of protein with simple dilution, but without alteration of the relative proportions of albumin, globulin and fibrinogen, is much more difficult. Verney suggested, since

the molecular volume of colloidal particles is comparatively large, that one may be dealing with a solution in a state analogous to that exhibited by a gas when highly compressed. In analogy, with van der Waal's equation of a gas, he found that the equation $p(v\text{-}b) = k$ in which p indicates osmotic pressure of the proteins, v, the reciprocal of protein nitrogen and b a constant, held for dilution of plasma up to 50 per cent of the original concentrations; in other words, the osmotic pressure of

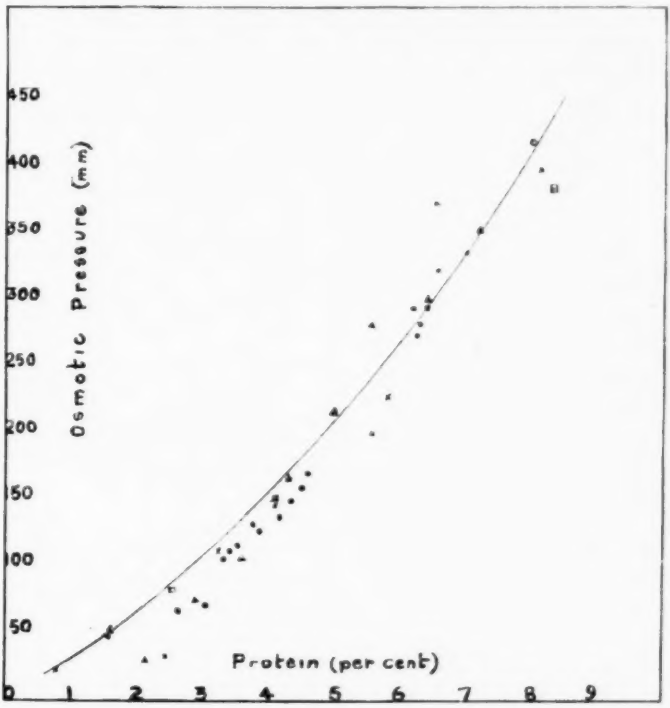

Chart 1.—Effects of dilution of blood proteins. The solid circle indicates results of Verney; the triangle, those of Fishberg; the cross, those of Mayrs (one blood); the line, those of Mayrs (mixed blood); the dot within the circle, those of Moore and Roaf; the dot within the square, those of Krogh and the star, those of Starling.

plasma proteins reacts to their dilution in a matter such as would be expected of a nonionized colloidal solution in which the colloidal particles occupied an effective volume as large as 50 per cent of the original.

It may here be noted that colloidal solutions belong to a class in which the values for osmotic pressure are less than those obtained with gram molecular solutions, namely, 22.4 atmospheres. These particles

are not in a molecular degree of dispersion, and therefore do not conform to Avogadro's law. Since it is the number of particles that determines the magnitude of the osmotic pressure, it would appear that with dilution of blood plasma there is greater hydration or aggregation, resulting in a smaller number of particles per unit of volume. This, however, is unlikely, since, as Svedberg stated, serum proteins tend to disaggregate into smaller particles on dilution.

Whatever the explanation may be, the fact remains that with dilution of serum or plasma, the colloidal osmotic pressure per gram of protein diminishes. Assuming the rate of change of pressure with respect to the concentration of protein to be proportional to the actual osmotic

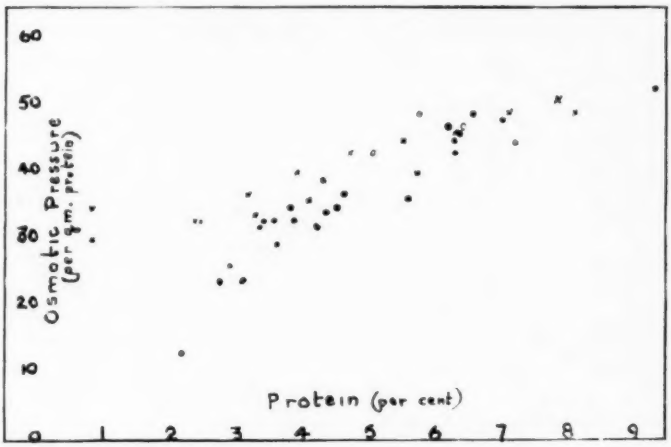

Chart 2.—Effects of dilution of blood proteins. The solid circle indicates results of Verney; the cross, those of Mayrs and the open circle, those of Fishberg.

pressure, Fishberg applied the differential equation $\frac{dp}{dv} = ap$, in which p indicates the reciprocal of the colloidal osmotic pressure, v, the reciprocal of the protein concentration and a, a constant depending on the total concentration of the proteins. In other words, $p = \epsilon^{av}$. Striking agreement was found between observed and calculated values.

In view of the foregoing observations, a series of patients exhibiting edema manifested by any one of the four signs already referred to were collected. In each case, the analyses of the blood included determinations of sugar, cholesterol, total protein and colloidal osmotic pressure.

Colloidal osmotic pressure was estimated according to the plan outlined by Mayrs;[7] in addition, aseptic precautions were taken as much as possible, since as Verney[8] pointed out, bacterial growth in either the serum or the dialysate may result in a decrease of pressure. The pressures are recorded in terms of millimeters of plasma, since in this inves-

tigation absolute values were not sought. The important information was the relationship between normal and pathologic blood and, as Mayrs pointed out, the necessary details, in order to express the osmotic pressure in terms of millimeters of water, would involve a much greater error than may be introduced by the densities of the various samples. All analyses were made at room temperature (18 C.), and readings were made eighteen hours after the bloods were exposed to dialysis. The technic involved in this determination is by no means simple. It has all of the difficulties inherent in work on membrane permeability in general. The greatest source of difficulty is the preparation of membranes of uniform permeability. In spite of this, when there is rigid adherence to details the error involved, according to Mayrs, ranges between 1 and 5 per cent.

The standards of colloidal osmotic pressure for given concentrations of total protein were the same as those employed by Mayrs in his work

TABLE 2.—*Effect of Dilution of Plasma on Colloidal Osmotic Pressure*

Plasma	Protein, per Cent	Colloidal Osmotic Pressure		
		Actual (a)	Expected* (e)	a/e × 100
Undiluted	6.62	290	312	92.9
80%	5.30	212	228	93.0
60%	3.98	146	155	94.2
40%	2.63	93	90	103.3
20%	1.32	37	40	95.5

* The expected values were obtained from chart 1. For statistical analysis the standards obtained from the continuous line in chart 1 will be referred to, hereafter, as the "expected" values; whereas, those experimentally determined will be referred to as the "actual" values.

on pathologic processes of the kidney.[7] Proof of the validity of these standards may be found in chart 1, in which are recorded, in addition to the data of another series of analyses by Mayers on a normal person, the observations of Verney,[8] Fishberg,[2] Starling,[6] Krogh[9] and Moore and Roaf.[10] The continuous line represents the standards used in this investigation and the dot line the data of the other authors referred to. The close agreement, particularly in the range of concentrations of protein met with clinically, is obvious.

It is obvious that unless the permeabilities of the membranes in these experiments approximated those by which the aforementioned standards were obtained, the data would hardly be comparable. Therefore, in order to test permeability, six samples of normal plasma were mixed together. The mixture was then diluted with Ringer's solution, and the diluted samples were tested with regard to their colloidal pressures with the results shown in table 2.

9. Krogh, quoted by Fishberg (footnote 2).

10. Moore and Roaf: Biochem. J. **2**:34, 1907.

It will be noted that the values tend to be slightly lower than the standards, but that the average difference is about 5 per cent. As Mayrs pointed out, however, though such graphs as the one employed may be found to be similar when obtained from the blood of normal persons, the levels may differ slightly. Small deviations must, therefore, not be stressed. Regardless, however, of the standards employed, there appears to be no reason for deviations to occur in a certain direction in one group of persons more frequently than in another merely from the operation of the laws of chance; and it may here be pointed out that the observations made in this paper are based on the deviations rather than on absolute values.

Though all of these subjects had some form of edema already mentioned, it will be noted that the protein concentrations, with the exception of those in nos. 8, 16 and 28, did not differ from the accepted normal values (Bodansky,[11] Van Slyke,[12] Wu,[13] Plimmer[14] and Hawk.[15] The

TABLE 3.—*Protein-Cholesterol Relationships*

Number of Observations	Protein, per Cent	Cholesterol, per Cent		
		Low	High	Average
2	6.00	0.219	0.277	0.248
4	6.01 – 6.50	0.238	0.396	0.286
8	6.51 – 7.00	0.222	0.427	0.324
11	7.01 – 7.50	0.232	0.574	0.365
3	7.51 – 8.00	0.302	0.426	0.354
4	8.01+	0.333	0.427	0.377

one subject (no. 8) with a definitely low protein had marked insulin edema. It therefore appears that though each subject had some edema, it was, apparently, not due to lowering of concentration of blood proteins. The high cholesterol values, therefore, do not appear to be the result of a compensatory phenomena, that is, the result of an effort to maintain a constant colloidal osmotic pressure.

These conclusions may be drawn from another observation. In table 3 are shown the relationships between the cholesterol and protein values. The protein values are grouped from low to high according to their concentrations, and their corresponding low, high and average

11. Bodansky, M.: Introduction to Physiological Chemistry, New York, John Wiley & Sons, 1927.

12. Van Slyke, D. D., and others: Proc. Soc. Exper. Biol. & Med. **20**:320, 1922-1923.

13. Wu, H.: J. Biol. Chem. **51**:33, 1922.

14. Plimmer, R. H. A.: Practical Organic and Bio-Chemistry, New York, Longmans, Green & Company, 1920.

15. Hawk and Bergeim: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, 1926.

cholesterol values are recorded. If the cholesterol values in these cases were due to a compensatory phenomenon, one would expect that as the total proteins decreased the cholesterols would increase. As a matter of fact, it appears that the cholesterol increased rather than decreased with increasing protein concentration.

TABLE 4.—*Ratios of Actual to Expected Colloidal Osmotic Pressures of Serum in Thirty-Two Cases of Diabetes Mellitus*

No.	Hospital No.	Per Cent			Osmotic Pressure (Mm. Serum)		
		Protein	Cholesterol	Sugar	Actual (a)	Theoretical (b)	$\frac{a}{b} \times 100$
1	7076-29	7.00	0.222	0.149	330	340	94
2	G.	7.17	0.240	0.119	393	348	113
3	73-30	8.31	0.416	0.140	497	440	113
4	7448-28	8.04	0.333	0.385	496	420	118
5	3953-29	6.91	0.537	0.208	405	332	122
6	2391-29	7.24	0.321	0.137	384	363	106
7	1312-29	7.08	0.232	0.333	373	345	108
8	Buch.	5.16	0.277	0.322	242	220	110
9	S. F.	6.73	0.308	0.156	333	320	104
10	6679-29	7.87	0.335	0.222	476	400	119
11	3953-29	6.65	0.427	0.201	363	313	116
12	7434-29	6.56	0.228	0.200	302	308	96
13	6000-29	7.17	0.427	0.087	414	348	119
14	3964-26	7.37	0.450	0.625	434	358	122
15	7447-29	6.74	0.273	0.059	358	320	112
16	7274-29	6.05	0.238	0.084	292	273	107
17	6038-22	8.14	0.333	0.204	496	425	116
18	1795-26	7.98	0.426	0.333	460	415	111
19	Rey.	7.25	0.500	0.149	431	365	118
20	3432-27	8.15	0.427	0.227	486	426	114
21	Dow.	7.35	0.304	0.126	405	365	111
22	McL.	7.61	0.302	0.188	429	383	112
23	2373-29	7.35	0.303	0.143	416	365	114
24	6037-29	7.43	0.326	0.123	418	370	113
25	See exp. 13	7.09	0.333	0.095	407	345	118
26	7420-29	6.13	0.268	0.125	287	280	102
27	7202-29	6.83	0.292	0.120	376	330	114
28	76-30	6.13	0.241	0.040	297	280	106
29	147-30	6.39	0.396	0.166	333	295	113
30	131-30	5.69	0.219	0.196	245	250	98
31	147-30	6.56	0.302	0.112	336	308	109
32	197-30	7.09	0.574	0.066	407	345	118

A possible fallacy in the interpretation of the foregoing data is that though the total protein values were normal, there may have been alterations of the relative proportions of albumin, globulin and fibrinogen. Though separate analyses of these three constituents of blood protein were not made, the data on the colloidal osmotic pressure oppose this view. It will be noted (table 4) that in the majority of cases the ratios of actual to expected pressures are not only above unity, but greater than can be accounted for by the percentage of error inherent in the technic.

From the foregoing data, it would, also, appear that diabetic patients with lipemia, as shown by a high content of blood cholesterols, tend to have higher colloidal osmotic pressures than do normal persons. If this conclusion is correct, it appears, as will be shown presently, that the observation made is of some clinical importance. To make more certain of this conclusion, the data were treated statistically.

In view of the small number of observations, the subjects were divided into three groups only, according to the cholesterol data. The average ratios of actual to expected colloidal osmotic pressure were calculated for each group, and the significance of these averages were judged by their probable errors. The results are shown in table 5. It will be noted that the ratio of the difference between the means of the

TABLE 5.—*Relationship Between Actual to Expected Osmotic Pressure and Cholesterol*

	Cholesterol, per Cent		
Actual Expected Osmotic Pressure*	—0.3	0.31-0.40	0.41+
Mean	105.0	113.2	117.0
σ	6.7	4.1	3.8
PE M	1.32	0.83	1.26
PE Δ	1.54	1.50	
$\frac{\Delta}{PE\,\Delta}$	5.1	2.5	

* The symbol σ indicates standard deviation; PE M $= \left(\frac{0.674}{\sqrt{n}}\right)$, probable error of mean; Δ = difference between means, and PE$\Delta = \left(\sqrt{(M_1)^2 + (M_2)^2}\right)$, probable error of differences between means.

different groups to the probable errors of their differences was such as to warrant the conclusion with reasonable certainty that the observations were not the results of operation of the laws of chance.

An obvious difficulty in the interpretation of the foregoing results is that it has been assumed that cholesterol concentrations parallel total lipoids. However, such parallelism has been shown to be the rule rather than the exception among diabetic patients, though among children hypercholesterolemia and lipemia are not, according to Boyd,[5] necessarily associated. Recently, however, Joslin [16] showed that though the quantity of fatty acid was tripled, the cholesterol was only doubled. According to this observation, the lipemia in diabetes is probably greater than indicated by the cholesterol alone; in other words, lack of parallelism not only does not minimize the value of these results, but enhances them.

16. Joslin, E. P.: The Treatment of Diabetes, ed. 4, Philadelphia, Lea & Febiger, 1928.

When shown these data, Professor Mayrs pointed out another possible difficulty with regard to their interpretation. As ratios of albumin to globulin were not determined, the possibility of high ratios must be considered, since relatively large amounts of albumin would tend to raise the colloidal pressure regardless of the lipoid content of the blood. In routine practice over a number of years, this laboratory has had occasion to determine such ratios, and none has ever been found to be high. Alterations of the relative proportions of albumin and globulin have invariably decreased rather than increased these ratios. In order, however, to exclude this objection as much as possible, four subjects were reexamined with the results shown in table 6.

These observations were made between three and four months after the first examination. This probably accounts for the different values obtained. It will be noted, however, that the phenomenon observed was the same, namely, higher ratios of actual to expected colloidal osmotic pressures associated with hypercholesterolemia. High ratios of albumin

TABLE 6.—*Results of Reexamination of Four Subjects*

Subject No.	Total Protein, per Cent	Albumin / Globulin	Cholesterol, per Cent	Osmotic Pressure		
				Actual (a)	Expected (e)	a/e × 100
3953-29	7.34	2.13	0.490	476	365	130.4
7448-28	7.62	1.86	0.520	434	384	113.0
3964-26	6.84	2.24	0.427	376	328	114.6
7202-29	7.31	1.79	0.347	416	360	115.5

to globulin are therefore excluded as a possible cause of high colloidal osmotic pressure, at least in the subjects investigated.

As the subjects investigated had edema, it was considered of interest to note the effects of markedly diluting blood with salt solution and compare them with the results of bleeding experiments reported by Fishberg. For this purpose, three diabetic subjects were selected. In two cases the diabetes was active; both showed marked emaciation. On admission, one patient (7420-29) had, in addition to glycosuria, marked acetonuria; the other (7434-29) had glycosuria only. The third subject (7447-29) had mild diabetes and was well nourished, but had gangrene of one of the feet. In each case, well salted broth was given at hourly intervals for a day. Each subject reacted differently to the experiment. The first (7447-29) took little salt and gained only 1 pound (0.5 Kg.) in twenty-four hours; the second (7420-29), a little more enthusiastic, took more salt and gained 9½ pounds (4.3 Kg.) during the same period. The third case (7434-29) was a classic. This subject took 64 Gm. of salt, drank 16,500 cc. of water and gained 22 pounds (10 Kg.) in twenty-two hours. In each of these cases, in addition to the data obtained in the other cases, plasma-cell ratios and the sodium chloride

content of the serum were also estimated. The chlorides were determined by the satisfactory method of Wilson and Ball.[17] The combined data are shown in table 7.

It will be noted in each case that at some time during the period of observation the blood was diluted according to the values of (*a*) the plasma-cell ratios and (*b*) the total protein concentrations. Allowing a technical error of 5 per cent, the actual and expected colloidal osmotic pressures, however, agreed fairly closely. Dilution of blood with saline, therefore, does not appear to result in compensatory lipemia. The serum chloride, it will be noted, though not great, was definitely greater after

TABLE 7.—*Effects of Ingestion of Large Quantities of Salt*

Protein, per Cent	Cholesterol, per Cent	Sugar per Cent	Osmotic Pressure			Plasma / Cells	NaCl per Cent			Weight, Pounds	No.
			Actual (a)	Theoretical (b)	a / b × 100						
6.13	0.268	0.125	319	280	114	0.85	0.520	Dec. 27	Forced fluids with salt		7420/29
5.86	0.326	.....	283	260	109	....	.....	Dec. 28		= 116½	
5.69	0.241	.....	265	250	106	....	.....	Dec. 30	30 Gm. NaCl	= 118¾	
4.49	0.228	0.125	176	182	97	2.12	0.566	Dec. 31		= 127¼	
5.43	0.232	0.212	221	235	94	1.21	0.552	Jan. 2		= 127¼	
5.95	0.241	0.125	273	265	103	1.14	0.560	Jan. 3		= 125¼	
6.56	0.228	0.232	329	305	108	1.00	0.550	Dec. 27			7434/29
6.83	0.214	.....	315	328	96	....	.....	Dec. 28		= 134	
6.90	0.232	.....	340	330	103	....	.....	Dec. 30	64 Gm. NaCl + 16,500 cc. water	= 134	
5.25	0.183	.....	207	225	92	1.41	0.640	Dec. 31		= 154	
5.95	0.169	0.200	262	267	98	1.23	0.555	Jan. 2		= 148¾	
6.12	0.169	0.208	283	275	103	1.03	0.566	Jan. 3		= 139	
6.74	0.273	0.059	355	320	111	0.92	0.566	Dec. 31	15 Gm. NaCl	= 155¼	7447/29
6.13	0.225	0.181	274	280	98	0.82	0.575	Jan. 2		= 154	
6.06	0.189	0.117	284	273	104	1.14	0.590	Jan. 3		= 156½	

ingestion of salt than can be accounted for by technical error inherent in the method employed.

There is another possible criticism of all of these observations, since, according to some workers, particularly German, blood proteins exert an insignificant osmotic pressure, if any. These authors believe that serum attracts water through a membrane of collodion because the proteins seek to imbibe water and be more hydrated; the condition is looked on as inhibition. Professor Mayrs[18] is also of the opinion that the blood lipoids can exert little osmotic pressure. They, as he pointed out, could do so only if in solution, and even then the amounts present

17. Wilson, D. W., and Ball, E. G.: J. Biol. Chem. **79**:221, 1928.

18. Personal communication.

do not appear to be great enough to account for the values found. This author makes the interesting suggestion that the phenomena observed might be explained by the lipoids reducing the permeability of the colloidin membranes. There is experimental basis for this suggestion; for example, Krogh obtained exceptionally high colloidal osmotic pressures by using membranes of low permeability. A control experiment suggested was to deproteinize diabetic and normal specimens of blood and compare the osmotic pressures of the remaining fluids. An objection to this procedure, however, is that during deproteinization one could hardly avoid altering the physical condition of such blood. Another suggestion was to compare the colloidal osmotic pressure of normal plasma plus lecithin emulsion in Ringer's solution with normal plasma plus Ringer's solution alone. With this experiment, the lecithin was not found to exert any osmotic pressure. Again, it may be observed that one can hardly simulate the physical state of blood lipoids with artificially prepared lecithin mixtures. As will presently be observed, however, the actual mechanism involved, that is, whether one is dealing with osmotic pressure, inbibition pressure or altered membrane permeability, is irrelevant; the fact that because of lipoids water is attracted or held in the sac is the important clinical consideration, as the following observations suggest, providing an analogy may be drawn between capillary walls and colloidin membranes.

If the prevalent view of urinary excretion is correct, that is, if hydrostatic pressure must overcome the resistance of some other form of pressure in the capillaries before glomerular filtration can occur, it follows that in diabetic patients with lipemia a greater hydrostatic force must be exerted if urine is to be excreted. Increased intra-arterial pressure, whether due to injection of epinephrine or continuous sympathetic stimulation, is alleged to produce arteriosclerosis in animals. One can hardly compare the marked resistance offered to the circulation in the latter types of experiments with the small amount possible as a result of increased colloidal osmotic pressure. Continued, however, over a long period of time, is this responsible for the marked incidence of cardiovascular disease in diabetes? Apropos of this suggestion, the data in table 8 are of interest. These subjects were selected for this investigation, not because of their blood pressures, but because of their edema and blood cholesterol. It is, therefore, interesting to note that of these thirty-two subjects, eighteen, an incidence of 56 per cent, had hypertension—an incidence too great even for diabetic subjects. (No. 28 is assumed to have hypertension, since a hemoglobin of 130 is too high for a boy 19 years of age.)

The relationships found between cholesterol (or lipemia) and anuria in diabetic coma are also suggestive. As is well known, diabetic patients

in or near coma tend to develop anuria. The latter, however, is not a constant observation. If raised colloidal osmotic pressure is a factor and if lipemia is the cause, one would expect to find some relationship between lipemia and anuria. As this was an afterthought, the degrees of anuria found in the past cannot be determined quantitatively, since no exact measures were made of the volume output of urine. Data on the urea are, however, available, as the determination of this blood constituent is a routine in all of our cases of coma. It appears reasonable to assume that, in the average, the more marked the anuria, the greater would be the concentration of urea in the blood, though a number of variables must also be considered, such as the duration of the coma, etc.

TABLE 8.—*Systolic and Diastolic Blood Pressures of All Subjects*

Subject No.	Age, Years	Blood Pressure		Subject No.	Age, Years	Blood Pressure	
		Systolic	Diastolic			Systolic	Diastolic
1	60	142	74	17	56	180	95
2	43	120	78	18	56	145	90
3	54	140	80	19	51	150	92
4	61	150	90	20	50	165	100
5	59	160	90	21	49	128	76
6	26	140	82	22	52	138	80
7	43	165	94	23	41	145	86
8	31	130	76	24	37	114	70
9	58	142	82	25	16	180	64
10	70	195	100	26	43	104	66
11	59	160	90	27	11	165	90
12	56	125	78	28	19	130	65
13	16	180	64	29	43	115	60
14	63	140	88	30	22	110	80
15	52	128	66	31	43	115	60
16	34	110	74	32	18	118	84

In table 9, are shown the necessary data to test this idea. Here are recorded the last thirty cases of diabetic coma of which our records are complete. In each case are recorded the age of the patient, the presence or absence of renal damage, the white blood cell count, blood sugar, blood urea and cholesterol and the degree of coma. The classification of the latter is arbitrary but serves for practical purposes and is as follows:

Degree	*State*
1	Drowsy
2	Semiconscious
3	Unconscious, but respond to painful stimuli
4	Completely unconscious

The data are grouped in table 10 in order to demonstrate relationship, if any, between the various phenomena. Briefly, it will be noted

that urea nitrogen and cholesterol were related. This conclusion is, it may be pointed out, based on averages. It is, therefore, a statistical conclusion and may, or may not, and need not necessarily, apply to any particular subject. Though there are, as stated, a number of variables to consider, these data tend to support the idea that in coma with lipemia

TABLE 9.—*Diabetic Coma*

				Urine		Blood				
No.	Hospital No.	Age, Years	Degree of Coma	Albumin	Casts	Sugar, per Cent	Cholesterol, per Cent	Urea Nitrogen, Mg. per 100 Cc.	White Blood Cells	Comment
1	197-30	18	2	+	+	0.464	0.574	15	34,000	
2	-30	20	2	+	+	0.625	0.241	11	27,400	Blood obtained after insulin
3	6419-29	11	1	+	+	1.200	0.687	35	26,200	
4	7420-29	44	1	+	+	0.277	0.577	18	5,600	Blood obtained after insulin
5	6123-29	22	3	+	+	0.769	0.640	32	24,000	
6	5041-29	55	1	+	+	0.416	0.660	71	12,200	
7	4525-29	65	2	+	+	0.333	0.214	22	28,800	Lobar pneumonia
8	4451-29	17	3	+	+	0.500	0.416	22	21,600	
9	4392-29	31	3	+	+	0.416	0.370	20	18,400	
10	4349-29	40	1	+	+	0.285	0.660	32	10,200	
11	4062-29	34	1	+	+	0.500	0.428	11	8,450	White blood cells on day after coma
12	2620-29	26	1	+	+	0.769	0.578	35	22,000	
13	431-29	49	2	+	+	0.277	0.341	15	.....	No white blood cells
14	254-29	69	1	+	+	0.476	0.402	31	10,000	
15	7411-28	15	2	+	+	0.625	0.980	38	10,100	
16	6738-28	23	4	+	+	1.100	1.158	36	16,000	Before admission; no coma on admission
17	6535-28	17	1	+	+	0.454	1.190	62	16,800	
18	5996-28	35	3	+	+	0.434	0.297	17	8,600	
19	6453-28	48	2	+	+	0.400	0.577	24	11,200	
20	5728-28	23	4	+	+	0.500	1.380	49	18,200	
21	5517-28	36	3	+	+	0.285	0.925	42	7,600	
22	1516-28	28	2	+	+	0.555	0.584	21	18,200	
23	121-28	76	2	+	+	0.769	1.140	82	15,800	
24	6244-27	30	1	+	+	0.555	0.428	13	7,850	
25	4569-27	27	3	+	+	0.584	0.562	28	14,600	
26	4203-27	2½	4	+	+	0.526	0.593	94	38,200	
27	2490-27	47	2	+	+	1.100	0.500	35	16,400	
28	958-27	58	4	+	+	1.000	0.483 +	101	18,400	Before coma
29	356-27	35	1	+	+	0.333	0.613	36	19,400	
30	336-27	48	1	+	+	0.295	0.624	49	22,400	

a greater hydrostatic pressure of blood is required to induce glomerular filtration.

In this connection it also is interesting to note that, according to Westphal, cholesterol is more readily extracted from blood with ether in diabetes and hypertension than in hypercholesterolemia associated with infections, pregnancy and nephrosis; in other words, there is further suggestive evidence that in diabetes and hypertension, cholesterol

exists in such a state as to exert its own osmotic pressure. This, it may be observed, fits in with the anomalously high colloidal osmotic pressure in hypertension quoted by Verney [8] from Govaerts (*Bull Acad. roy. de méd. de Belg.*).

SUMMARY AND CONCLUSIONS

Though this investigation failed so far as finding an explanation for certain high cholesterol values occasionally met with in diabetic blood is

TABLE 10.—*Relationships Between Blood Sugar, Cholesterol, Urea Nitrogen, Leukocytes and Severity of Coma in Thirty Cases of Diabetic Coma*

Average	Blood Sugar		
	—0.4	0.41 – 0.80	0.81+
Cholesterol	0.566	0.637	0.707
Urea nitrogen	30	36	52
White blood cells	15,000	18,000	19,000
	Cholesterol		
	—0.4	0.41 – 0.80	0.81+
Sugar	0.417	0.579	0.622
Urea nitrogen	17	37	51
White blood cells	20,000	18,000	15,000
	Urea Nitrogen		
	—25	26 – 50	51+
Sugar	0.445	0.726	0.720
Cholesterol	0.385	0.740	0.813
White blood cells	17,240	16,000	22,000
	Leukocytes		
	—10	11 – 25	25+
Sugar	0.421	0.604	0.429
Cholesterol	0.500	0.728	0.462
White blood cells	22,000	43,000	35,000
	Severity		
	1	2	3	4
Sugar	0.505	0.572	0.500	0.781
Cholesterol	0.586	0.572	0.535	0.903
Urea nitrogen	36	29	27	70
White blood cells	14,200	20,000	15,000	22,000

concerned, a new phenomenon was observed. It is suggested that though there is relatively little direct evidence, the sum of all available data (clinical and laboratory) tends to support the view that in diabetes with lipemia there is constantly exerted in the capillaries a colloidal pressure greater than the normal. To overcome the latter for purposes of renal excretion, a greater hydrostatic pressure is required; this increased pressure, though relatively small, when continued over a long period of

time probably has the same effect as more marked intracapillary pressure exerted over a short period of time. In animals the latter, when produced either by injection of epinephrine or by sympathetic stimulation, is alleged to cause arteriosclerosis. Is this, therefore, a cause of the marked incidence of cardiovascular disease in diabetes? The data are recorded, in order that the theory may be tested by others with similar facilities available.

ADDENDUM

During the course of further experiment and since this paper was submitted for publication, an interesting observation was made with regard to the colloidal osmotic pressure of lipemic blood which is of sufficient interest to be added to this report.

As is well known, the plasma of diabetic blood may, while still fresh, be clear, in spite of a fat content of from 2 to 3 per cent or more; but when such blood is exposed to ordinary room temperature over a period

TABLE 11.—*Effects of Physical State of Blood Fat on Colloidal Osmotic Pressure*

Date	Total Protein	Total Fat	Cholesterol	Colloidal Osmotic Pressure		
				Actual	Expected	Actual / Expected
May 21.....	6.50	1.90	0.423	342	300	114.0
May 22.....	6.43	1.82	0.421	285	295	96.6

of from twelve to twenty-four hours, it may become cloudy, and the cloudiness is due to fat globules. Why one lipemic blood should be turbid and another clear is imperfectly understood. Bloor, I believe, was the first to record this phenomenon and termed it "masked lipemia." This author also suggested that it depends on the physical state of the fat.

The interesting observation with regard to colloidal osmotic pressure is that in one such case of masked lipemia accidentally observed recently the ratio of actual to expected colloidal osmotic pressure was high when the plasma was clear, whereas it was normal the following day, when the plasma became turbid on standing at room temperature.

These observations would suggest that when the blood was first withdrawn and the plasma was clear, the lipoids were in solution and could then exert an osmotic pressure; whereas on standing, when the blood became cloudy the fat was in suspension and, therefore, could not exert an osmotic pressure. The first idea that occurred to me was that the blood while standing at room temperature had undergone proteolysis. Though slight proteolysis did occur, it does not entirely explain the decrease of osmotic pressure (table 11).

THE EFFECTS OF INTRAVENOUS INJECTIONS OF FOREIGN PROTEIN ON PEPTIC ULCER *

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The present study is an attempt to interpret the effects of intravenous injections of nonspecific foreign proteins on patients with peptic ulcer. We studied the effect on gastric secretion, hoping to obtain data that might be of value in elucidating the genesis of pain in gastric and duodenal ulcer. We also wish to record our observation of the therapeutic effects of foreign protein in peptic ulcer.

Previous observers reported improvement of symptoms, especially relief from pain, following injections of protein. Pribram [1] noted that in forty-two of seventy-seven patients pain stopped immediately at the end of treatment. A month after the injections were stopped, thirty-eight remained free from pain. At the end of eight months, there was subjective cure in thirty-two cases, but in seven of these, although there was no pain, there were pyrosis and a feeling of weight. Pribram analyzed the gastric juice in thirty-one of his cases. Under the influence of injections of protein, the acidity became normal in eighteen; in seven it decreased without becoming normal, and in six the hyperchlorhydria increased. Kalk [2] studied the curve of secretion in seventeen patients; in seven the acidity and duration of secretion remained unchanged; in four there was a slight decrease, and in only one a marked decrease. Von Friederich [3] found that treatment with foreign protein had little effect on the acidity. Martin [4] recently reported his experiences, and remarked that "The first change one notices during treatment is a marked decrease in pain." In a group of seventeen cases observed immediately

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1. Pribram, B. O.: Parenterale Reizbehandlung des Magen und duodenal Geschurs, Med. Klin. **18**:958 (July 23) 1922.

2. Kalk, H.: Erfahrunger mit protein-korper Therapie des Ulcus duodeni und ventriculi, Klin. Wchnschr. **2**:1310, 1923.

3. von Friedrich, Ladislaus: Protein Therapie der peptischen Geschure, Arch. f. Verdauungskr. **34**:75, 1925; Zur Frage der protein Therapie des Magen und duodenal Geschur, München. med. Wchnschr. **72**:458, 1925.

4. Martin, Lay: Peptic Ulcer: The Effect of Parenteral Injections of Purified Milk Proteins on Symptoms and Progress, Arch. Int. Med. **43**:299 (March) 1929.

after treatment, there was an increase in acidity in five, an approximate constancy in nine and a true decrease in three. Of twenty-eight cases, eight were observed after a period of from four to eighteen months, and among these, there was an increase of acid in two, an approximate constancy in two and a decrease in four. It is interesting to note that of the four patients showing a decreased acidity, three are reported as clinically well, and an operation was performed on the fourth. The two patients who showed a "constancy of acidity" are also reported as being clinically well, while of the two with an increase in acidity, one was operated on and showed a healed duodenal ulcer and the other was reported as being worse.

PRESENT STUDIES

Eleven patients were studied. The clinical diagnosis of peptic ulcer (gastric or duodenal) was made from a careful analysis of the history, the symptoms and the physical signs, such as localized tenderness, positive roentgen shadows and positive gastric analysis and analysis of the stools.

The patients selected for study were on a general ward diet, except that meat was excluded. They were not confined to rest in bed, but were allowed to walk about the ward as they desired.

A control fractional gastric analysis was made on each patient in addition to the Ewald test meal, which was given as a routine procedure.

An intravenous injection of foreign protein was given the following day. The first dose contained from 500,000,000 to 800,000,000 gonococcus or typhoid vaccine (we found that gonococcus vaccine gave a much more severe reaction than typhoid vaccine, and therefore we used it in the greater number of cases). If the reaction following the initial dose was severe, the dose on subsequent injections was the same. If the reaction was mild or moderate, the dose was increased to 1,000,000,000, then to 1,500,000,000 and finally to 2,400,000,000. Five or six injections were given to each patient. The interval between each injection was from five to seven days.

Fractional gastric analysis was made on each patient twenty-four and forty-eight hours following each injection, and whenever possible from one to two weeks after the final injection. The temperature was recorded every four hours on the day of the injection and for two days after.

Roentgenograms and fluoroscopic examinations were made before the first and after the last injection. Analysis of the stools were made throughout the entire period of observation.

Tables 1 to 4 illustrate the changes in acidity of the gastric juice following intravenous injections of foreign protein. Our results showed

TABLES SHOWING RESULTS OF FRACTIONAL GASTRIC ANALYSES IN PEPTIC ULCER BEFORE AND AFTER INTRAVENOUS INJECTION OF FOREIGN PROTEIN

TABLE 1.—*Acidity Reduced with Relief from Pain—Cases 1, 2, 3 and 4; Case 2, Typhoid Vaccine Used*

	Control Fractional		After Typhoid Vaccine, 500,000,000 Temperature 99.5 F.				After Typhoid Vaccine, 1,000,000,000 Temperature 100 F.				After Typhoid Vaccine, 1,200,000,000 Temperature 101 F.				After Typhoid Vaccine, 1,500,000,000 Temperature 102.6 F.				After Typhoid Vaccine, 1,500,000,000 Temperature 101.4 F.				Fractional 9 Days After Last Injection	
			24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours			
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty	..	..	30	41	21	31	50	63	20	31	26	39	45	52	41	47	50	61	27	33	0	18	20	30
Aspir.	96	101																						
1st	42	51	32	44	11	21	18	25	0	22	30	36	20	27	15	22	18	24	12	16	12	16	15	24
2d	46	54	68	77	22	28	33	40	30	38	38	44	15	23	26	34	32	40	20	28	20	28	18	16
3d	60	71	42	58	55	65	55	63	60	71	50	59	40	52	50	57	43	51	31	40	30	41	16	25
4th	62	72	48	59	50	60	45	56	52	61	56	61	49	61	61	69	52	60	35	42	35	42	11	19
5th	70	83	60	72	42	51	45	59	60	73	57	65	64	76	44	52	38	44	56	65	56	64	30	38
6th	65	80	..	..	30	43	36	43	68	77	59	66	60	68	50	59	50	63	20	35	20	29	25	36

TABLE 2.—*Acidity Reduced with Little or No Relief from Pain; Case 7, Gonococcus Vaccine Used*

	Control Fractional		After Gonococcus Vaccine, 600,000,000 Temperature 100.2 F.				After Gonococcus Vaccine, 800,000,000 Temperature 102.2 F.				After Gonococcus Vaccine, 1,200,000,000 Temperature 101 F.				After Gonococcus Vaccine, 1,500,000,000 Temperature 103.4 F.			
			24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty	60	66	26	38	Not obtained		22	36	50	59	34	49	18	34	24	37	32	46
1st	46	56	16	25	..	..	40	49	10	19	29	38	15	28	19	26	18	25
2d	72	79	14	27	..	..	42	53	11	22	40	56	45	54	25	34	21	29
3d	83	96	28	39	..	..	43	51	38	46	62	69	22	35	35	42	30	42
4th	89	98	40	53	..	..	42	52	60	68	61	70	36	42	45	56	26	35
5th	62	69	36	44	..	..	20	33	71	84	70	78	52	62	42	51	42	51
6th	64	70	29	37	..	..	52	68	79	87	51	63	46	54	32	40	29	38

TABLE 3.—*Acidity Unchanged—Pain Relieved—Cases 5, 8 and 9; Case 5, Gonococcus Vaccine Used*

	Control Fractional		After Gonococcus Vaccine, 600,000,000 Temperature 104.6 F.				After Gonococcus Vaccine, 800,000,000 Temperature 101.8 F.				After Gonococcus Vaccine, 1,200,000,000 Temperature 102 F.				After Gonococcus Vaccine, 1,500,000,000 Temperature 103 F.				After Gonococcus Vaccine, 2,000,000,000 Temperature 101.6 F.				Fractional 2 Weeks After Injections	
			24 Hours T. 102.6 F.		48 Hours T. normal		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours			
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty	33	49	10	20	15	28	30	41	50	59	42	54	20	28	15	20	55	65	68	79	36	47	25	34
1st	38	47	38	46	32	40	26	32	40	48	58	66	68	73	55	61	68	76	74	82	68	79	40	50
2d	50	61	56	64	40	47	38	42	52	59	69	77	73	80	60	68	77	84	70	79	56	62	46	53
3d	52	63	52	61	49	57	61	70	45	56	63	72	67	74	51	62	73	80	72	80	63	73	48	55
4th	45	57	44	52	55	62	54	61	66	73	84	98	56	66	62	69	70	77	79	88	71	80	41	52
5th	32	36	58	79	60	71	51	62	62	70	79	85	40	48	57	66	48	60	78	87	73	82	49	63
6th	12	18	75	86	33	37	60	72	72	84	62	68	51	60	52	63	56	63	67	81	73	86	40	49

TABLE 4.—*Acidity Increased—Pain Relieved—Case 10, Gonococcus Vaccine Used*

	Control Fractional		After Gonococcus Vaccine, 500,000,000 Temperature 103.4 F.				After Gonococcus Vaccine, 600,000,000 Temperature 99 F.				After Gonococcus Vaccine, 800,000,000 Temperature 104 F.				After Gonococcus Vaccine, 850,000,000 Temperature 103 F.				After Gonococcus Vaccine, 800,000,000 Temperature 102 F.			
			24 Hours		48 Hours T. normal		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty	12	21	0	6	4	16	4	16	Not obtained		No free		0	6	6	16	Refused		0	12	0	6
1st	0	14	0	8	0	8	0	8	..	..	acid in		0	8	5	14	to be		0	9	6	14
2d	18	26	9	14	6	12	7	18	..	..	any speci-		4	13	11	18	aspirated		8	20	0	9
3d	19	29	11	19	10	18	8	18	..	..	men		20	28	19	28	..	..	12	26	10	19
4th	15	27	10	18	9	15	11	19	..	..	..	..	32	47	26	34	..	..	23	29	16	29
5th	21	29	0	11	0	11	0	9	..	..	..	..	43	52	21	30	..	..	20	32	18	27
6th	16	25	8	21	5	19	9	15	..	..	..	..	38	40	26	32	..	..	16	22	15	26

TABLE 5.—*Acidity Unchanged in Control*

	Control Fractional		After Gonococcus Vaccine, 500,000,000 Temperature 102.2 F. 24 Hours T. 101.8 F.		After Gonococcus Vaccine, 500,000,000 Temperature 102.2 F. 48 Hours T. normal		After Gonococcus Vaccine, 900,000,000 Temperature 103.2 F. 24 Hours		After Gonococcus Vaccine, 900,000,000 Temperature 103.2 F. 48 Hours		After Gonococcus Vaccine, 1,200,000,000 Temperature 102.4 F. 24 Hours		After Gonococcus Vaccine, 1,200,000,000 Temperature 102.4 F. 48 Hours		After Gonococcus Vaccine, 1,500,000,000 Temperature 101.4 F. 24 Hours		After Gonococcus Vaccine, 1,500,000,000 Temperature 101.4 F. 48 Hours		After Gonococcus Vaccine, 1,500,000,000 Temperature 100.4 F. 24 Hours		After Gonococcus Vaccine, 1,500,000,000 Temperature 100.4 F. 48 Hours		Fractional 5 Days Later	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty.....	75	85	35	45	43	53	63	75	Not obtained		30	39	35	43	65	72	Not obtained		30	49	45	55	46	58
1st.....	31	43	25	36	23	28	15	27	..	..	36	43	32	40	50	61	..	..	42	53	36	42	38	49
2d.....	50	58	35	45	26	56	23	36	..	..	63	72	48	59	74	82	..	..	49	60	43	50	56	64
3d.....	74	86	36	42	27	52	30	41	..	..	61	70	62	71	60	71	..	..	52	64	60	68	63	72
4th.....	48	59	34	46	65	73	60	69	..	..	50	62	70	82	60	69	..	..	60	71	93	86	60	74
5th.....	53	60	39	50	51	62	65	72	..	..	62	70	62	70	56	63	..	..	62	72	66	74	71	80
6th.....	64	73	32	39	43	55	65	72	..	..	41	58	70	79	52	61	..	..	48	57	72	80	56	66

that the gastric acidity was decreased in five patients, unchanged (or very little change) in four and increased in one.

In four patients a reduction in acidity was observed, and this was associated with relief from pain. In one patient (case 7, table 2) a definite reduction in acidity occurred but no relief from pain and no improvement. In the patients in cases 5, 8 and 9 (table 3), there was no change in the gastric acidity, but the pain was relieved and the patients were improved. In the patient in case 10 (table 4), who was suspected of having carcinoma, and who had initial low acidity, the acidity was increased and the pain was relieved for from twenty-four to forty-eight hours. In a patient with gastrojejunal ulcer, the acidity was reduced, but complete studies were not made.

COMMENT

Meyer, Cohen and Carlson [5] studied the effects of fever on gastric secretion in dogs and noted a marked depression in acidity during the fever. Foreign protein was used in these experiments. These observations were conducted during the febrile period, and it was noted that there was a marked diminution in the free, total hydrochloric acid and volume of gastric juice, and that on the following day, when the animals were free from fever, the secreting response was normal. In a measure, our present observations on patients coincide with the observations on dogs. We were unable to obtain gastric analysis at the height of fever (in some cases as high as 104.2 F.), but occasionally the rise in temperature persisted after a reaction, as in case 9.

We were inclined to believe that a possible explanation of the immediate relief from pain was the diminution in the gastric acidity and gastric secretion occurring at the height of the fever. Assuming that this diminution occurred in all cases in which the patients were treated with foreign protein, the return to a normal acidity in a period of from twenty-four to forty-eight hours with relative freedom from pain would be evidence against acidity as the cause of pain. More convincing evidence against acidity as a prime factor is the presence of pain following a definite reduction in acidity (all other causes of pain, such as cholecystitis, chronic appendicitis, etc., having been ruled out). This, as we have pointed out, was well illustrated by the patient in case 7. In a like manner, we find it difficult to explain the relief from pain following a definite increase in acidity (case 10).

That gastric tonus and gastric hunger contractions are the important factors in the mechanism of pain in ulcer is a view held by many

5. Meyer, Jacob; Cohen, Seymour J., and Carlson, A. J.: The Effect of Fever on Gastric Secretion, Arch. Int. Med. **21**:354 (March) 1918.

observers (Hurst, Ginsburg and his associates, Carlson and Ivy [6]). Pribram said that in addition to its other effects foreign protein acts on the vagus and sympathetic system, causing relaxation of the spasm. He noted that following the injection of novoprotein, epinephrine causes no change in the pulse rate and blood pressure, and he concluded from this that the excitability of the nervous system is diminished by the injection of protein. Both Holler [7] and Pribram [8] reported that pylorospasm is abolished by foreign protein, and that the decrease in spasm is so marked that a stenosis, which was thought to be due to anatomic deformity, disappeared. Von Friedrich does not believe that the improvement in gastric function is due to relaxation of the pyloric spasm, but that during an attack of pain, the musculature of the stomach is in a condition of hypotonia, comparable to that of a myocardium in a condition of decompensation. Under the influence of novoprotein, the condition became

TABLE 6.—*Showing Return to Normal Acidity with Normal Temperature*

			Given Gonococcus Vaccine, 500,000,000			
			Temperature 102 F.		Temperature Normal	
	Control		24 Hours		48 Hours	
	Free	Total	Free	Total	Free	Total
Empty	67	80	11	24	62	71
1st	41	54	7	16	21	34
2d	88	93	29	34	34	42
3d	57	69	36	47	63	71
4th	38	44	41	49	80	89
5th	60	72	38	45	63	76
6th	78	86	39	47	73	84

normal and effective, like that of a myocardium under the influence of digitalis. This hypothesis, however, is contradicted by the observations of Müller and Petersen,[9] who showed that nonspecific protein causes a

6. Hurst, A. F.: The Sensibility of the Alimentary Canal, London, Oxford University Press, 1911. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Contributions to the Physiology of the Stomach: XXXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916. Carlson, A. J.: Am. J. Physiol. **45**:81, 1917. Ivy, A. C.: Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

7. Holler, Gottfried: Ist eine organische Vaguserkrankung die Ursachen des Ulcus ventriculi chronicum beim Menschen, Wien. klin. Wchnschr. **34**:223, 1921.

8. Pribram, B. O.: Protein Therapie und chirurgische Therapie des Magenschurs, Klin. Wchnschr. **2**:2112, 1923.

9. Müller, E. F., and Petersen, W. F.: Ueber die Wirkung der Proteinkorperinjektion auf den Mageninnervation, München. med. Wchnschr. **74**:531, 1927.

diminution of the gastric contractions in man. Likewise, Meyer and Carlson,[10] while studying hunger and appetite during fever in dogs, showed that there was a complete absence of hunger contractions following injections of sodium nucleinate. Meyer and Carlson were of the opinion that the fever or the toxins appear to induce a lowering of the vagus tone and thus lead to a cessation of the hunger contractions.

In view of these observations, we are of the opinion that a similar lowering of vagus tonus and a diminution of gastric tonus and gastric contractions occur in man following injections of protein and are important factors in the relief from pain.

Is the relief from pain, following the injection of foreign protein, associated with the improvement of the circulation in the stomach and the increased vascularity about the ulcer? Clinicians have noted the relief from pain in peripheral vascular disease, as in thrombo-angiitis obliterans following the intravenous injection of foreign protein. In these cases the relief from pain is due to increased vascularity and improved collateral circulation. Is it likely that the relief from pain in ulcer is due to a similar phenomenon? We believe this to be the case. We wish to present the hypothesis that pain from ulcer is associated with variations and disturbances in the blood supply in and about the ulcer. It is generally assumed that the ingestion of food relieves the pain from ulcer, because it diminishes tonus and neutralizes acidity. We wish to advance the hypothesis that pain is diminished because the ingestion of food increases the general vascular supply of the stomach, particularly about the area of the ulcer. Consequent on this increased vascular supply there is a diminution in tonus and spasm and therefore relief from pain. The return of pain in from one-half to one hour or longer after food, we explain thus: as digestion proceeds, there is an increase in vigor of the peristaltic activity; this increased activity depletes the vascular bed of the rugae of the stomach, particularly in the ulcer-bearing area, and results in local asphyxia, edema, spasm and pain. This hypothesis, it seems to us, offers a reasonable explanation of the rhythmic character of pain in peptic ulcer. Likewise it presents an explanation of pain from ulcer independent of the degree of acidity. We explain the relief from pain obtained by the ingestion of alkalis by the observations of pharmacologists[11] that dilute solution of alkalis may act as an irritant to the gastric mucosa, improving the circulation and thus relieving the pain and distention.

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10. Meyer, Jacob, and Carlson, A. J.: Hunger and Appetite in Fever, Am. J. Physiol. **44**:222 (Sept.) 1917.

11. Cushny, A. R.: Pharmacology, ed. 9, Philadelphia, Lea & Febiger, 1928, p. 572.

CLINICAL OBSERVATIONS

A clinical analysis of the therapeutic effects is necessarily limited by many factors that enter into the control of patients, particularly of the class referred to the Cook County Hospital. Emphasis is therefore placed on the fact that the present therapeutic report is one of observations of clinical progress rather than end-results. It is also particularly emphasized that the period of observation was not sufficient to warrant conclusions as to end-results.

We feel it important to call attention to the following facts:

Relief from Pain.—As many other observers, we also find that the relief from pain following injections is a striking feature. The relief from pain is apparently not dependent on the severity of the constitutional reaction or the degree of temperature. The analgesic effect was noted in every instance, in periods varying from eighteen hours to several months after injections. Two patients showed striking relief following the first injection for the entire period of observation; two showed moderate relief after the first injection (of these, one had a carcinoma of the stomach). Pribram was of the opinion that the intravenous route is the best. It would seem, however, from the results of others, that subcutaneous injections produce similar therapeutic effects. Our excuse for using the intravenous method was our interest in observing the effect on the acidity. We did not encounter any untoward effects.

The Effect on Patients with Definite Bleeding.—Four of the patients studied gave a history of profuse bleeding. One patient had severe melena for six months and again three weeks before admission; one patient with gastrojejunal ulcer had a constant 4 + blood reaction in the stool, and one patient had a carcinoma of stomach with a constant 4 + blood reaction in the stool. One patient had a definite history of hematemesis. None of these might be considered as having acute gastric hemorrhage. It did not appear that the constitutional reaction or the possible changes in the tissues about the ulcer, which are said to occur after injections of protein, were of such a nature as to produce an increase in bleeding; on the contrary, blood disappeared from the stools during and after treatment in all of the patients except the one for whom a diagnosis of carcinoma was made. This was particularly striking in the patient with a gastrojejunal ulcer.

Effect on Roentgen Deformities.—As we remarked, all of our patients showed a definite duodenal or gastric defect fluoroscopically and by x-ray films before we accepted them for study. Fluoroscopy was performed in every instance at the end of the course of treatment, but we were unable to note any marked change in the gastric defects. In one instance, the gastric defect seemed smaller. No case showed complete disappearance of the deformity.

Terminal Results.—One patient (case 2) had a recurrence one week after a course of five injections. He was operated on, and a shallow gastroduodenal ulcer was found situated at the pyloric ring and extending to the duodenum. In another patient, symptoms recurred six weeks after the course of intravenous treatment. In two patients, no symptoms were noted seven and six months, respectively, after injections, and in another, nine months after treatment. Seven months after the injection, the x-ray film in the last patient still showed the duodenal defect.

CONCLUSIONS

1. Relief from pain during treatment for peptic ulcer obtained by intravenous injections of foreign protein is independent of changes in acidity.

2. We believe that the diminution in gastric tonus and contractions which occurs following injections of foreign protein is an important factor in the relief from pain.

3. The increased vascularity in the stomach and in the capillary bed in and about the ulcer is the important factor in relief from pain.

4. We wish to advance the hypothesis that rhythmic pain in ulcer is due to rhythmic variations and disturbances in the vascular bed in and about the ulcer, associated with digestive peristaltic activity.

5. Nonspecific protein is to be considered only as an adjunct in the treatment for peptic ulcer.

THE BOLTZ TEST IN URINALYSIS*

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This test was first described by Boltz [1] in 1923 as a simple and specific spinal fluid test for dementia paralytica. Grossman,[2] in 1925, and Harris,[3] in 1926, essentially confirmed this report, Grossman adding that the white of an egg also gives a positive reaction. Walker and Sleeper,[4] in 1927, questioned the accuracy of the previous results, and offered convincing evidence, mainly of a chemical nature, that the test is not specific. They stated that a positive reaction is due to a reaction between an aldehyde and tryptophan. In 1928, Myerson and Halloran [5] reported that they had found that in spinal fluid a positive Boltz reaction is obtained whenever there has been an increase in protein from whatever cause, the degree of positivity corresponding closely with the quantitative increase in protein. They stated that it is not a specific test for dementia paralytica, and that it is positive in spinal fluid in the presence of protein; but they offer no conclusive evidence that the positive reaction in spinal fluid is due to proteins alone, or that proteins play the principal part in the reaction. They recommend the use of the acetic anhydride of Powers, Weightman and Rosengarten, which contains a relatively large amount of aldehyde, present as an impurity. The work of the authors mentioned indicates that the positive reaction results from the presence of an amino-acid, presumably tryptophan.

It came to my attention by accident that this test might be applied directly to the urine, and this report is based on the examination of 167 normal and 525 pathologic specimens.

TECHNIC

(*a*) Place in a small glass test tube 1 cc. of the filtered or centrifugated specimen to be examined.

(*b*) Add 0.3 cc. of acetic anhydride, preferably a brand high in aldehyde content, from a pipet, a drop at a time, with shaking.

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* Submitted for publication, May 17, 1930.

* From the Clinical Laboratory of the McLeod Infirmary, Florence, S. C.

1. Boltz, O. H.: Am. J. Psychiat. **3**:111, 1923-1924.
2. Grossman, S.: J. Ment. Sc. **21**:439, 1925.
3. Harris, J. S.: Brit. M. J. **1**:136 (Jan. 23) 1926.
4. Walker, B. S., and Sleeper, F. H.: J. Lab. & Clin. Med. **12**:1048 (Aug.) 1927.
5. Myerson, A., and Halloran, R. D.: J. Nerv. & Ment. Dis. **68**:155 (Aug.) 1928.

(*c*) Add 0.8 cc. of concentrated sulphuric acid, from a pipet, a drop at a time, with shaking.

(*d*) Let the tube stand at room temperature under observation for five minutes.

The positive reaction is indicated by the appearance of a light lilac to deep purple color. Occasionally, in weak positive reactions, the positive color may appear within the five minute period and subsequently be obliterated by the darker colors due to the reaction of other substances in the urine. Occasionally, in strongly positive reactions the positive color may not appear before the expiration of some minutes, owing to the darker colors produced immediately by the reaction of other substances in the urine. In strongly positive specimens the purple color may be so dark as to require dilution of the preparation with water in order to differentiate the purple from possible dark browns or blacks. The prescribed five minutes of the test is a valid test period, as positive specimens have been shown to hold the positive color for several hours. The test with urine is practically impossible to read by any of the artificial lights with which I have experimented up to the time of writing.

EXPERIMENTAL OBSERVATIONS

I have been unable to produce a positive Boltz reaction with aqueous, alcoholic or ethereal extracts of dehydrated beef heart powder, or with cholesterol in solution in these liquids, or with cholesterol in solution in any of these extracts of dehydrated beef heart, or with cholesterol in solution in urine.

I have checked Grossman's positive observation with the white of an egg. I have also produced positive Boltz reactions with aqueous solutions of trypsin and with casein.

The substance producing the positive Boltz reaction in urine is destroyed by bacterial growth. In weakly positive specimens, it may disappear in a few hours. In strongly positive specimens, it may still be demonstrated after several days. The substance may be preserved in urine by the addition of a sufficient amount of any of the following reagents to inhibit bacterial growth: chloroform, ether, phenol. The positive reaction is interfered with by the addition of an excess of phenol. Formalin in the proportion of 1 cc. of the 40 per cent commercial product per ten cubic centimeters of the specimen immediately destroys the substance. The substance is precipitated and preserved by the addition of mercuric chloride.

NORMAL OBSERVATIONS

The specimens reported on in the accompanying table were obtained from voluntary controls—physicians, interns and laboratory workers. The time periods covered by the examinations ranged from one week for controls 8 and 10 to sixty-two days for controls 2 and 3. The specimens were obtained at varying hours of the day, but at intervals of at least eighteen hours. During the total period covered by the examinations, controls 2, 3, 6, 9 and 10 were on essentially the same diet; the other controls were on different diets.

The single positive specimens from controls 3 and 7 were very faintly positive by the test. Control 5, who showed six positive specimens of twenty taken during a period of sixty-one days, reported that he had suffered from a mild nephritis several years previously. Control 6 was a rather neurasthenic person, who stated that he believed himself to be suffering from some metabolic insufficiency of an unknown nature, as he was entirely unable to gain weight though he habitually ate large quantities of food.

I concluded from this series that in the normal human man on an average diet, no amino-acid detectable by the Boltz test should be eliminated in the urine.

PATHOLOGIC OBSERVATIONS

The pathologic series comprised examinations of 525 specimens: 161 were from medical cases, of which 35 per cent were found to have positive Boltz reactions; 332 were from surgical cases, of which 33 per

Normal Control Series

Control		Total Specimens Examined	Specimens Having Positive Boltz Reactions
1	Laboratory worker (male)	32	0
2	Physician (male)	25	0
3	Intern (male)	23	1
4	Physician (male)	21	0
5	Physician (male)	20	6
6	Intern (male)	19	4
7	Physician (male)	14	1
8	Laboratory worker (male)	6	0
9	Intern (male)	4	0
10	Intern (male)	3	0

cent were positive; 32 were from obstetric cases, of which 16 per cent were positive. The highest positive observation was 72 per cent in the group of specimens from patients with degenerative diseases of the kidneys. Another highly positive observation among the medical groups was 46 per cent of the specimens from patients with acute infections. The highest positive observation in the surgical groups was in specimens from cases of appendicitis, the percentage being 42. The small number of specimens from uncomplicated obstetric cases showed no positive observations.

The high incidence of the positive Boltz reaction of 72 per cent of all specimens from patients with degenerative diseases of the kidneys would seem to indicate that the primary significance of the positive test is that the kidneys have been affected. In this group the positive Boltz reaction was always accompanied by the finding of albumin. This was far from the case, however, in considering the observations in the pathologic group as a whole. The high incidence of positive Boltz reactions of albumin-free specimens—46 per cent of all the positive Boltz reactions, or 15 per cent of all the specimens examined—clearly suggests

that the test may be more useful than the test for albumin to disclose early or latent conditions of the kidney, and further investigation of this possibility is to be desired.

Another inference of significance may be drawn from the following figures: Of the group of specimens taken from patients with chronic and acute infections, 32 per cent with the positive Boltz reactions were albumin-free; of the group of specimens taken from patients on whom appendectomy and miscellaneous laparotomy, including salpingectomy, had been performed, 58 per cent with the positive Boltz reactions were albumin-free; of the specimens from patients with nervous and mental diseases, 80 per cent with the positive Boltz reaction were albumin-free; in the traumatic cases, 85 per cent of the specimens with positive Boltz reactions were albumin-free. A positive Boltz reaction would therefore seem to be a significant physical observation in nervous and mental diseases and in cases of shock. Two of the cases encountered in the series were worthy of mention.

CASE 1.—J. N., came into the outpatient clinic on Sept. 29, 1929, with an undiagnosed fever. A strongly positive Boltz reaction was the only positive observation.

CASE 2.—The clinical study of the terminal case of Mr. S., admitted to the clinic on Sept. 20, 1929, yielded no information leading to a diagnosis. The strongly positive Boltz reaction in the urine was the most sifinificant observation. Provisional diagnoses of carcinoma of the gallbladder and chronic cholecystitis complicated by lobar pneumonia were advanced, but not confirmed entirely as permission for an autopsy was refused.

SUMMARY AND CONCLUSIONS

The Boltz acetic anhydride reaction is discussed, and its application in urinalysis is reported. Results of the examination of 167 normal and 525 pathologic specimens are given.

The Boltz test is a valuable adjunct to urinalysis that demonstrates the elimination of an amino-acid.

Evidence is offered indicating that the test may be more valuable than the test for albumin to demonstrate an early or latent condition of the kidney, though further investigations are to be desired in order to make this evidence conclusive.

Evidence is offered indicating that the positive Boltz reaction in urine is of particular significance in nervous and mental cases and in shock.

ANTIBODY FORMATION IN KALA-AZAR *

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Numerous attempts have been made to show that antibodies originate in the hematopoietic system. It has been found that stimulation of the hematopoietic system by bleeding or by other methods causes an increase in the production of demonstrable antibodies. On the other hand, injury to the blood-forming organs by overexposure to x-rays or radium or by the injection of large dose of benzine or other poisons usually results in a diminished production of demonstrable antibodies. Animals thus treated are also less immune to experimental infection. Furthermore, it has been shown [1] that patients with chronic diseases of the blood-forming organs (aplastic anemia, lymphatic and myelogenous leukemia) show little or no antibody response following the injection of various bacterial antigens.

While such evidence tends to show that the blood-forming organs play the chief rôle in the formation of immune bodies, other investigators emphasize the importance of the reticulo-endothelial system as the chief site of antibody origin. Evidence for the latter contention is not conclusive. The reports of many experiments designed to show variations in the antibody response after "blocking" the reticulo-endothelial system with various colloidal substances are conflicting. It has also been shown [2] that experimental typhus fever, a disease characterized by rather widespread proliferation and degeneration [3] of the endothelial system without much evidence of damage to the blood-forming organs, has little or no influence on immunity or on the formation or behavior of certain demonstrable immune bodies. These results tend to reduce the importance of the reticulo-endothelial system as the chief site of antibody origin.

Further studies were made on patients with kala-azar, a disease characterized by marked proliferation of the endothelial tissue of the liver, spleen, lymph nodes and bone-marrow. In no other disease is the

* Submitted for publication, May 3, 1930.

* From the Department of Medicine, Peiping Union Medical College.

1. Rotky, H.: Zentralbl. f. inn. Med. **35**:953, 1914. Howell, K. M.: Failure of Antibody Response in Leukemia, Arch. Int. Med. **26**:706 (Dec.) 1920. Howell, K. M., and Schultz, O. T.: Proc. Inst. Med., Chicago **5**:52, 1924.

2. Reimann, H. A., and Wu, C. J.: J. Immunol. **18**:159, 1930.

3. Bauer, E.: München. med. Wchnschr. **63**:541, 1916. Hertzog, G.: Centralbl. f. allg. Path. u. path. Anat. **29**:97, 1918.

intensity of the endothelial reaction so great. In addition, the hematopoietic system is also injured, as is shown by the marked anemia, leukopenia and thrombopenia that occur. There is also histologic evidence of a lack of erythropoiesis in the bone-marrow.[4] Clinical evidence clearly indicates a marked depression of immunity. Cancrum oris and other secondary infections commonly occur and frequently terminate fatally. Studies were then made to determine the nature of the demonstrable immune response (agglutinins) to the injection of typhoid vaccine in nine Chinese patients with kala-azar. For purposes of comparison, one patient who had recovered from kala-azar a few months previously, six healthy young adults and two patients with chronic myelogenous leukemia were similarly vaccinated and studied.

METHOD

Triple typhoid vaccine containing 500,000,000 *Bacillus typhosus* and 250,000,000 each of *Bacillus paratyphosus* A and B per cubic centimeter, prepared by the National Epidemic Bureau of Peiping, was used. Subcutaneous injections of 0.5 cc., 1 cc. and 1 cc. were made at five day intervals. Blood was withdrawn for examination before vaccination, after the second vaccination and thereafter at approximately ten day intervals for two months or more. The serum was separated, and agglutination tests were performed according to the standard macroscopic technic. All patients with kala-azar were under treatment with urea stibamine and recovered during the period of observation.

EXPERIMENTAL OBSERVATIONS

In general, a striking difference in the immune response was noted between the patients with kala-azar or leukemia and the healthy subjects. The temperature was frequently increased shortly after vaccination, but no unusual effects were observed on the number of any of the blood cells in the patients with leukemia or kala-azar. In most cases the immune response to *B. paratyphosus* A was greatest and to *B. typhosus*, poorest.

Agglutinin Formation in Normal Persons.—Many studies have shown that agglutinins for typhoid bacilli in normal persons increase rapidly after vaccination, and that two weeks after the third injection they sometimes reach a titer of 10,000 or 20,000. The titer may be maintained at a high level for one or two months, then begins to decline slowly and is often still demonstrable a year or two later. In order to establish controls for the vaccine and for the technic used in the experiments on patients with kala-azar, six normal young adults were vaccinated and observed. The agglutinins for all three strains appeared promptly and rose rapidly in most instances to 5,120 but

4. Meleney, H. E.: Am. J. Path. **1**:147, 1925.

usually fell off rather rapidly to 1,280 or 640, and then more slowly until at the end of two months they were 320 or 160. As in the observations reported later, the agglutinin response to *B. paratyphosus* A was usually the strongest and that to *B. typhosus* the weakest. In one person *B. paratyphosus* A agglutinin titer reached 5,120 while that for *B. typhosus* never exceeded 320 and disappeared in thirty days.

Chart 1 represents typical agglutinin titer curves in a normal subject. For convenience the chart is drawn to a different scale than chart 2, and does not emphasize the striking difference in immune response between the patients and the normal persons studied.

Agglutinin Formation in Kala-Azar.—Agglutinins for one or more of the three strains were formed in all vaccinated cases even if in low

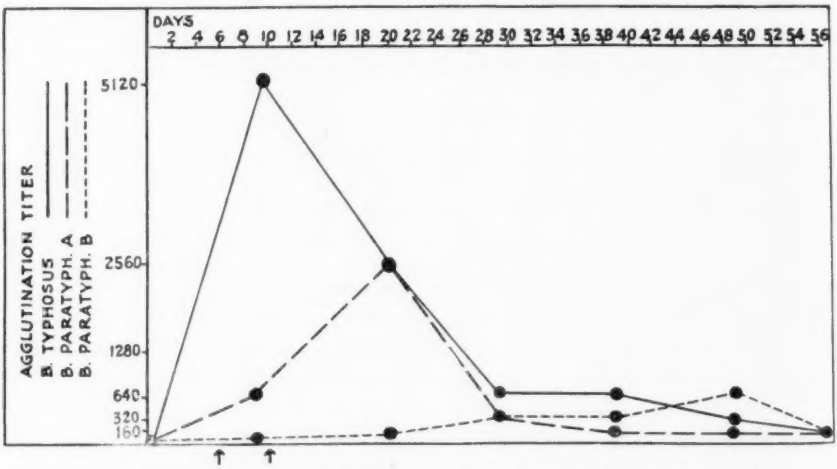

Chart 1.—The average agglutinin response in a normal subject vaccinated with triple typhoid vaccine. The ordinate is drawn to a different scale than in chart 2. The arrows indicate the time of vaccination.

titer. In four of the nine cases the titer for *B. paratyphosus* A reached 640 in two or three weeks after the first injection, and then rapidly diminished. In one case the titer reached 1,280, the highest observed in the patients with kala-azar, but rapidly fell off to 80 in three weeks. By the end of two months the titer diminished to 80 or 160 in three patients and had disappeared in five others.

The agglutinin titer for *B. typhosus* or *B. paratyphosus* B never exceeded 320 in any of the patients with kala-azar. In three cases agglutinins for *B. typhosus* failed to appear at all. At the end of two months, agglutinins for these strains were present at a titer of 80 in three patients and were not demonstrable in five others.

Chart 2 illustrates a typical experiment. The agglutinin response to all three strains was low in this case and disappeared within thirty days after the first vaccination. A large staphylococcus abscess formed on the thigh toward the end of the disease. In spite of the abscess, no stimulation of antibodies occurred.

One patient in whom vaccination was begun during the last few days of illness and finished when his temperature was normal, showed a fairly high response (640) to all three strains after the first vaccination. Three weeks later, while the titer was diminishing, he developed acute pharyngitis and furunculosis. Immediately following this the titer for *B. typhosus* rose to 2,560 and for *B. paratyphosus* A and B to 5,120, and it was still present at 640 four weeks later.

The agglutinins of a patient included in this study who had recovered from kala-azar six months previously responded to vaccination like the normal subjects used for controls. The hospital record of another

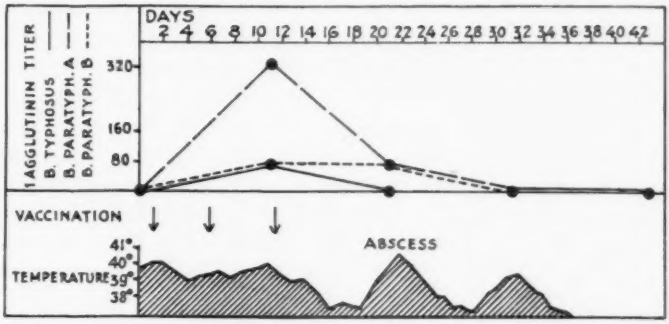

Chart 2.—The low agglutinin response and early disappearance of agglutinins in a patient with kala-azar vaccinated with triple typhoid vaccine.

patient who developed typical typhoid fever during kala-azar was found. The blood culture was positive for *B. typhosus*, but agglutinins did not appear as late as twenty-seven days after the onset.

Agglutinin Formation in Myelogenous Leukemia.—It has already been shown that during leukemia, a disease of the blood-forming organs, there is a marked depression of agglutinin response to bacterial antigens. These observations were confirmed by the results observed in two patients with chronic myelogenous leukemia included in this study. One patient had a normal erythrocyte count and a leukocyte count of 60,000, and he had been ill for two years. He had been treated repeatedly with radium. Ten days after vaccination with the triple typhoid vaccine, the agglutinin titer for *B. typhosus* and *B. paratyphosus* A reached 640. Thereafter it rapidly declined and was not demonstrable twenty days later. The agglutinin titer for *B. paratyphosus B* never exceeded 40.

The second patient was in a more serious condition, with 3,000,000 erythrocytes and 260,000 leukocytes per cubic millimeter of blood. He had been ill for one year and was declining. After vaccination the agglutinin titer in his serum for *B. typhosus* never exceeded 80 and soon disappeared entirely. Agglutinins for *B. paratyphosus* A and B failed to appear.

COMMENT

The clinical impression of diminished resistance to secondary bacterial invasion during kala-azar is corroborated by experimental laboratory evidence of a depression of the immune response to injected bacterial antigens. A similar depressed response occurred in vaccinated patients with leukemia. Although specific agglutinins were found in all cases following vaccination, they were much weaker in titer and disappeared much sooner than the agglutinins of similarly vaccinated normal controls. Both kala-azar and leukemia are diseases that affect the blood-forming organs profoundly. Therefore, since immunity and demonstrable antibody formation are depressed during these two diseases, evidence is at hand that indicates a relationship between the hematopoietic system and the formation of immune bodies. During or after recovery from kala-azar, as shown in two patients observed in this study, the normal ability to form agglutinins returns.

In spite of the numerous investigations thus far made, it still seems impossible to locate the exact site of origin of antibodies, or even to determine if an exact site actually exists. Evidence is at hand indicating that the hemotopoietic system is at least an important source. It has been shown that procedures that stimulate blood formation may simultaneously increase antibody titer and that procedures that injure the blood-forming organs may cause a simultaneous depression of antibody formation. However, in many of the experiments tried and in the diseases studied, it is difficult to estimate the rôle of the reticulo-endothelial system or other systems that also may play important parts. It is difficult to gage the amount of actual harm done to the reticulo-endothelial system as well as to the hematopoietic system following overexposure to x-rays or the injection of poisons. Furthermore, in kala-azar and in leukemia the endothelial system is also profoundly affected, so that it is impossible to conclude that injury to the hematopoietic system alone is responsible for the diminished antibody formation.

CONCLUSION

There is a marked depression of the immune response to typhoid vaccination in patients with kala-azar and leukemia. After recovery from kala-azar, agglutinins are again formed normally.

ERYTHROCYTE SEDIMENTATION TEST IN TUBERCULOSIS

A STUDY OF TWO THOUSAND CASES *

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The recent medical literature contains numerous reports dealing with the clinical application of the erythrocyte sedimentation test, an excellent review of which may be found in a valuable study of Peterman.[1] The conclusions drawn from these works concerning its specificity, reliability and usefulness in the diagnosis and prognosis of tuberculosis are far from being unanimous. For this reason we feel that the information derived from the study of this test in 2,000 consecutive cases at Muirdale Sanatorium might be worth recording.

The phenomenon that red blood cells suspended in solutions of anticoagulants, such as sodium citrate, potassium oxalate, hirudin or heparin, settle down with increasing rapidity in a great many pathologic conditions has been utilized in the recognition of certain diseases since 1897. The efforts of Fahraeus to detect pregnancy by means of the sedimentation test in 1918 were followed by reports from practically all branches of medicine.

Among the various explanations of the varying rate of sedimentation of erythrocytes, the following two seem to be the most plausible: (1) an increase in the fibrinogen content of the blood plasma and (2) changes in the number and size of the erythrocytes.

Red blood cells settle down very rapidly in solutions of high fibrinogen content, and several investigators have shown that in diseases characterized by fast sedimentation a definite increase in the fibrinogen content of the plasma can be found. Toxin production as it occurs in many inflammatory and destructive diseases will involve a breaking down of tissue proteins, and subsequently the products of disintegrated tissue proteins, particularly that of the lung tissue, will stimulate fibrinogen formation. One of our best coagulants used as a routine measure in the treatment for pulmonary hemorrhage is Mill's fibrogen prepared from extract of lung tissue. Changes in the amount and composition of blood

* Submitted for publication, April 10, 1930.

* From Muirdale Sanatorium.

1. Peterman, M. G., and Seeger, S. J.: Sedimentation Reaction in Children, Am. J. Dis. Child. **37**:693 (April) 1929.

proteins are detectable in tuberculosis as the result of the influence of bacterial toxins and broken-down pulmonary tissue particles. It is found that the total amount of protein may be normal or increased in tuberculosis or decreased if marked cachexia is present. The amount of globulin becomes abnormally high while the albumin reaches very low levels. The average fibrinogen content of the blood in normal persons is 0.2 per hundred cubic centimeters. Gram [2] reported fibrinogen values from 0.25 to 1.22 in tuberculosis.

Diminution in the number, volume and hemoglobin index of the erythrocytes may result in an increased sedimentation speed, while opposite results will cause a slower sedimentation.

Before discussing the results of the sedimentation test in tuberculosis, it is important to point out the variations of the sedimentation rate in normal blood described by many authors. The sedimentation rate is higher in infants and young children than in adults and in women than in men; it is increased during menstruation and during digestion. Variations were demonstrated by several authors in healthy persons under external application of heat and following ultraviolet ray and roentgen radiation. Some reports even show wide variations under apparently physiologic conditions at different times during the day in the same person. On the other hand, Loehr [3] claimed that though such variations may occur, they usually fall within the normal range. In our work we did not find the so-called physiologic variations during a day or from day to day to have any significance concerning the result and interpretation of the test, and we believe that they do not detract from its value and can be entirely disregarded in routine clinical work. At the same time it is necessary to emphasize the fact that no correct evaluation of this test is possible unless the external or incidental factors enumerated as having a possible influence on the sedimentation rate are eliminated or discounted.

Equal emphasis must be laid on exactly controlled uniform technic, whatever method is used. It must be kept in mind that the sedimentation speed will be increased when the test is performed at high room temperature. Venous stasis and tilting of the tubes will also increase appreciably the sedimentation rate. Of the different procedures, the Westergren method was adapted with some modification as follows:

TECHNIC

Draw 3.8 per cent sterile sodium citrate solution to the 0.4 cc. mark of a 2 cc. syringe previously washed with the same solution, taking care to shake out all air

2. Gram, H. C.: On Causes of Variation in Sedimentation of Corpuscles and Formation of Crusta Phlogistica ("Size," "Buffy Coat") on Blood, Arch. Int. Med. **28**:312 (Sept.) 1921.

3. Loehr, Hans: Klin. Wchnschr. **1**:483, 1922.

bubbles. Draw blood either directly from the patient's vein or from a tube of fresh blood. Fill the syringe to 2 cc., making the ratio of citrate to blood 1:5. Then allow a 0.1 cc. bubble of air to enter, and invert the syringe several times permitting the bubble to travel back and forth, thus mixing the blood and citrate solution. The blood is now ready to be transferred into a sedimentation tube which is a 1 cc. clear glass container, open at both ends and graduated into 100 equal parts like the barrel of a Luer tuberculin fornier. Before the tube can be used it has to be sealed at the base with a mixture of equal parts of paraffin and petrolatum melted together. The wax is packed into the tube up to where the graduation begins. The tube is held upright in a large sized rubber stopper. Let one or two drops of the blood mixture run first to the very bottom of the sedimentation tube, and the rest will follow easily without blocking the narrow opening. When the tube is full as nearly as possible to the 1 cc. mark, record the exact time, and set the interval timer to ring in fifteen minutes, when the first reading is made. Other readings follow in half an hour (from the time the test was started), one, two and twenty-four hours.

The results are recorded on a graph on which the time is indicated along the horizontal line and the percentage reading of the red blood cell level along the vertical line. To make comparison simple, a minimal normal curve, based on the sedimentation rates of eighty healthy persons, is always shown on this graph. The readings of the normal curve are 97, 95, 90, 75, 40, at the time intervals above mentioned; readings above this series are, of course, normal too. For the sake of convenience and brevity, the whole series of readings may be stated as one figure which actually represents the percentage of a test as compared with the minimal normal curve. For example, add the figures 97, 95, 90, 75, 40 given above and 3 (an arbitrary number) and divide the sum by 4; the result equals 100. Compare the normal with a test reading, 90, 75, 60, 50, 40 (add 90, 75, 60, 50, 40, 3 and divide by 4): the result is 79. In other words, this test is only 79 per cent of the normal.

Concerning its applicability in tuberculosis, the following questions should be answered:

1. Is it a specific reaction?
2. Is it an indicator of activity?
3. Is it an index to the extent and character of the tuberculous lesion?
4. Does it have any prognostic value?
5. Can it be used for the control of the course of the disease, including the detection of new foci and complications, and for judging the results of treatment?

OBSERVATIONS

It was pointed out that increased fibrinogen content of the blood, parallel with an increased sedimentation rate, may occur in a great many inflammatory conditions and in patients with malignant tumors. Of the 2,000 cases included in this study, the types of nontuberculous cases showing rapid sedimentation were as follows: pulmonary cancer, chronic unresolved pneumonia, pulmonary actinomycosis, chronic bronchitis, pulmonary syphilis, allergic asthma, pulmonary gangrene,

bronchiectasis, pulmonary abscess, subacute bacterial endocarditis, rheumatic endocarditis, Pick's disease, rheumatic polyarthritis, hypertrophic arthritis, Hodgkin's disease, exophthalmic goiter, syphilis, gonococcic sepsis, Still's disease, chronic pyelitis, chronic osteomyelitis, purulent otitis media, tonsillitis, sarcoma of the tibia and aplastic pernicious anemia. It is necessary to emphasize the frequency with which rapid sedimentation occurs in many pulmonary diseases other than tuberculosis. In addition to these diseases, senile dementia, neurosyphilis, general paralysis, epilepsy, malaria, leprosy, pneumonia, Addison's disease, acute arthritis, malignant conditions in general and inflammatory conditions of the genito-urinary system have been reported by others as causing increased sedimentation. It was found that jaundice and anemias cause a retardation of the rate. Yet we had under our care a patient with aplastic pernicious anemia who showed a marked increase in the rate of sedimentation. It can be said, therefore, that an increase in sedimentation velocity does not indicate tuberculosis unless all of the conditions mentioned can be excluded. A test that changes from so many causes should be utilized with utmost caution for the diagnosis of tuberculosis.

While it is generally accepted that rapid sedimentation in itself does not necessarily indicate tuberculosis, many investigators have expressed the opinion that a normal sedimentation rate excludes active tuberculosis. On the basis of our observations we doubt that so much reliability can be placed on this test without jeopardizing diagnostic exactness and the benefits of early and appropriate treatment. Among the 2,000 patients admitted to the sanatorium with a tentative diagnosis of tuberculosis since the routine use of the sedimentation test was established at Muirdale, 128 were found who had active tuberculosis, pulmonary, extrapulmonary or both, diagnosed by physical examination and corroborated by roentgen and laboratory observations, and whose sedimentation rate on repeated examination was normal. This figure is high enough to warrant a detailed analysis of these cases.

The group includes seventy-seven male and fifty-one female patients, varying in age from 2 to 59 years, of whom eighty-nine were adults and thirty-nine were children. The proportion in the colored race was found to be much lower than that in the general population of the sanatorium. This fact has no definite explanation except an innate lessened tissue resistance against the destructive effect of the tuberculotoxins or the lack of adequate immune body formation in these patients. Out of the total number with normal sedimentation rate, eighty-one patients had had frank parenchymal lesion of the lungs, fourteen having minimal, fifty-four moderately advanced and thirteen far advanced processes. In comparison with the percentage distribution in these three stages among all our patients, as taken from the sanatorium statistics for the year 1928,

which was 7.1, 47 and 45.9 in minimal, moderately advanced and far advanced cases respectively, the percentage in the group that we are analyzing is 17.28, 66.66 and 16.04. These figures show a marked increase in the minimal and moderately advanced cases and a considerable decrease in the far advanced cases. The accompanying table illustrates the frequency of positive sputum, the occurrence of different types of lesions and the presence of cavities in this group.

Positive sputum was found in 21.42 per cent of the cases of minimal, 38.88 per cent of those of moderately advanced and 76.92 per cent of those of far advanced lesions. From this data, it is evident that normal sedimentation velocity and positive sputum may coexist. Since this possibility detracts from the reliability of the sedimentation test in diagnostic work, it should serve as a warning against the enthusiasm of those who consider a normal rate as evidence of the absence of active tuberculosis. A method with such working error should not be considered equal in value to the demonstration of tubercle bacilli in the sputum,

Analysis of Cases of Tuberculosis

Classification	Number	Positive Sputum	Fibrotic	Exudative	Cavity	
					Single	Multiple
Minimal	14	3	3	11		
Moderately advanced	54	21	6	48	7	1
Far advanced	13	10	1	12	2	2
Total	81	34	10	71	9	3

or a trustworthy criterion for ruling out tuberculosis, unless all other information—clinical, roentgenographic and laboratory—is corroborative in the same sense. Let us add that in all these patients with positive sputum the bacilli were detected by the simple Ziehl-Neelsen procedure without homogenization.

Another noteworthy observation recorded in this group was that 87.65 per cent of the patients presented an exudative type of lesion on admission and only 12.35 per cent were found to have the fibrotic type of disease. Close analysis of clinical and roentgenographic observations disclosed these data.

To find normal sedimentation velocity in a group of exudative lesions is rather conspicuous and contrary to expectations. Knowing that inflammatory processes are liable to upset the physicochemical balance of the blood, causing a change in the colloidal composition of plasma proteins and an augmentation of the globulins and fibrinogen, one would reasonably suppose an increase in the rate in this type of pulmonary tuberculosis. The exudative process is characterized by typical inflammatory changes that can be visualized as a tuberculous pneumonic patch with a potential tendency to caseation, tissue disintegration and cavity

formation or absorption or fibrotic tissue formation. There is no doubt that whatever course the inflammatory condition takes, during its existence toxins are absorbed and are present in the blood; yet in these cases this does not effect any change detectable by the sedimentation test.

It is much more plausible to presume that the sedimentation rate in a certain number of fibrotic processes is a manifestation of less toxicity, higher resistance and a prompter defense mechanism.

As an approach toward the explanation of this exception to the apparent rule of abnormal sedimentation rate in pulmonary tuberculosis, it can be pointed out that the course and prognosis of the disease in this group was more favorable than was found in similar stages of pulmonary tuberculosis in general, indicating a probable better immunity and more stable physiologic equilibrium of the body. In the eighty-one patients with normal sedimentation velocity and manifest pulmonary tuberculosis, the condition was apparently arrested in twenty-six or 32.09 per cent, became quiescent in fourteen or 17.28 per cent, improved in thirty-two or 39.5 per cent and remained unimproved in only six or 7.4 per cent; three or 3.7 per cent died.

The transition from caseation to cavity formation was not rare in this group. Of fifty-four moderately advanced cases, a single cavity was demonstrable in seven and multiple cavities in one. Of thirteen far advanced cases, multiple cavitation was found in two and a single cavity in two. The cavities varied in appearance from honey-combing to spaces from 2 to 4 cm. in diameter. The finding of cavities contributes additional weight to our impression that the use of the sedimentation test for the exclusion of tuberculosis has considerable limitations.

Tuberculous and nontuberculous complications were found among these patients as follows: plastic or exudative pleurisy in six, rectal fistula in three, intestinal tuberculosis in two, tuberculous arthritis in one, mitral stenosis in one, tertiary syphilis in one and diabetes in one.

On the basis of symptoms presented on admission the majority of the patients could not be considered as having benign tuberculosis. Slight cough with expectoration was recorded in thirty-eight, moderate or severe cough with expectoration in thirty-three. The amount of sputum varied from a slight quantity to 120 cc. per day. Cough without expectoration was found in one case, and only in nine cases was the absence of cough and expectoration noted. Almost half of the group complained of pains in the chest. Slight or moderate dyspnea on exertion was seen in forty-four, and marked dyspnea in only four patients. Hemoptysis occurred in thirty-two patients, nine of whom had major pulmonary hemorrhage and two repeated hemoptysis. The temperature taken by mouth during rest periods ranged as high as 40 C. (104 F.) in

eight patients; in nine patients it reached 38 C. (100.4 F.) or more, and in twenty-two between 37.5 (99.5 F.) and 38 C. The remainder of the patients had temperature ranging from normal to 37.5 C.

Physical observations characteristic of active parenchymal infiltration were recorded in each case, the most frequent being impaired percussion sound, abnormal breath sounds and moist râles. No râles could be heard over the lungs of four patients with minimal and two patients with moderately advanced disease. The diagnosis for these six patients was based on other physical observations, roentgen and laboratory evidence. In the majority of instances the physical and roentgen observations were congruous. Occasionally clinically silent areas were demonstrated by roentgen rays.

In fifty cases of the group in which hematologic studies were made simultaneously with the sedimentation test, secondary anemia was found in twenty-five, the lowest red blood count being 3,570,000 with 50 per cent hemoglobin; the highest leukocyte count encountered was 17,900. Lymphocytosis was frequently seen and the number of cases with a marked increase in the monocyte-lymphocyte ratio was small. Evidently more information could be derived from the blood picture than from the sedimentation rate in this group.

Hilar tuberculosis with a normal sedimentation rate occurred in nineteen children. Normal sedimentation speed was shown in six cases of tuberculous pleurisy and one case of tuberculous peritonitis. Of the fifty-nine orthopedic patients, normal values were found in thirteen. And, finally, eight cases of tuberculous lymphadenitis presented normal sedimentation graphs. These observations suggest that a normal sedimentation rate is not a reliable sign of the absence of extrapulmonary forms of tuberculosis.

Of the 2,000 cases analyzed, normal sedimentation tests were found on admission in 387. This number includes 128 patients with manifest active tuberculosis whose detailed description has been given. The remaining 259 represent cases of upper respiratory catarrh, chronic bronchitis, emphysema, allergic asthma, bronchiectasis, traumatic pulmonary hemorrhage, pneumonoconiosis, convalescence from infectious diseases with respiratory complications, exophthalmic goiter, diabetes, chronic osteomyelitis, rickets, postpoliomyelitic scoliosis, tabes, familial optic nerve atrophy, psychoneurosis, chronic pyelitis, myocarditis, malnutrition and no disease; the two latter groups include many contact children who were referred to us for preventorium care.

It can be seen, therefore, that of the 1,741 tuberculous cases, 128 or 7.35 per cent having evidence of active tuberculosis showed normal sedimentation curves. Discounting this shortcoming of the method, we found that the activity of the process has a direct influence on the sedi-

mentation rate in the great majority of instances. Exceptions to this rule occur. An interesting example was the case of a man, aged 51, admitted to the sanatorium with the characteristic toxic symptoms of tuberculosis, including afternoon chills, fever and night sweats, in whose sputum tubercle bacilli were found; the physical and roentgen examinations revealed typical miliary tuberculosis. The man died three weeks after admission, although his sedimentation rate was 94 per cent, that is, not far from normal. Other examples of extensive exudative lesions with or without cavitation, with positive sputum and marked subjective symptoms and nearly normal sedimentation could be cited; yet we may say that these are the exceptions and not the rule and tend to call attention to these facts: 1. Active tuberculosis usually is accompanied by disturbed colloid balance of the blood, which may be demonstrated by the increased sedimentation rate of the red blood cells. 2. Slight or moderate deviations from the normal rate may have great practical significance and should not be left out of consideration.

It is important to emphasize the fact that not so much the extent of the lesion as the toxicity of the infection is the main factor influencing the sedimentation rate. We observed many patients whose pulmonary involvement was extensive, yet whose sedimentation speed was comparatively slow; on the other hand, we often saw limited lesions with very rapid sedimentation. When toxic symptoms dominate, a rapid sedimentation rate can be expected. Fibrotic processes with less marked symptoms are less liable to show a great difference from normal, whereas virulent infections, with considerable soft infiltration, destruction and cavity formation, are accompanied by an abnormally rapid rate. A very low graph, that is, a very rapid rate, should always be considered an important sign of marked activity, and should serve as a guide in outlining a therapeutic plan for our patients. We have frequently had the opportunity to observe that the sedimentation rate was a more sensitive index of the presence of large amounts of toxins in the body than the temperature or pulse rate. Therefore, it seems desirable that a study of this test be included in the analysis of every case when patients are advised in questions of rest, exercise or further clinical supervision.

No generalized answer can be given to the question of the prognostic value of the sedimentation procedure. Any one familiar with the pathology and nature of tuberculosis, with the variable results of the antagonistic effects of bacterial poisons, decomposed tissue proteins, on one hand, and the body's tendency to resistance, defense and repair, on the other hand, will realize that a single test reflecting a moment's status of the dynamic conflict between body and germs can hardly foretell the outcome of a long series of changes occurring in tuberculosis. Still it may be said with all fair-mindedness that sedimentation velocity slightly

or moderately above normal does not have a great significance in this direction. A number of patients who died at the sanatorium presented slightly or moderately higher values than normal on admission. More significance can be attached to a marked increase in speed when it is found repeatedly during the course of the illness. Such results can be considered of grave prognosis.

The greatest merit of this procedure, however, lies in its usefulness in observing the course of the disease, as a sensitive indicator of complications or the development of new foci and as a criterion of results of general routine or any special treatment. Naturally, the prerequisite for obtaining such information is the repetition of the test at regular intervals or from time to time whenever such information is needed, with an accurate standardized technic.

In general, the disappearance of toxic symptoms, the improvement of the patient's physical condition and the decrease in clinical observations are accompanied by a sedimentation rate approaching normal. An increase in toxicity, progress of the disease and a continuously failing physical condition bring an increase in the speed of sedimentation. New foci in the lung tissue are sometimes hidden to diagnostic approach for a considerable length of time, and complications like intestinal or renal tuberculosis are often unsuspected; the increased rate in such cases may direct the attention to the source of disturbance and may enable us to apply appropriate measures. Periodic repetition of this test in cases of pneumothorax, phrenic nerve block and heliotherapy is of extreme value. It not only renders possible the early recognition of complications like pleural effusion or empyema, but, what is even more important, it offers an approximate gage of the extent of improvement when physical or roentgen examination would be of little value. It has been emphasized that minor deviation from normal may indicate gross activity. Therefore, no patient should be classified and discharged as having a quiescent or apparently arrested condition unless his sedimentation rate has returned to normal. It would be advisable to determine the rate of every patient discharged from a sanatorium or under the supervision of a dispensary in connection with each periodic examination.

CONCLUSIONS

1. A study of the sedimentation test in 2,000 patients is reported.

2. Exactly controlled standardized technic and repetition of the test at intervals are essential features of the procedure. Presentation of readings in graphic form and their comparison with the minimal normal graph renders possible an easy visualization of the results. It proved highly practical in our work to record the readings in one figure which represents the percentage of the minimal normal rate.

3. The test cannot be used in the diagnosis of tuberculosis unless pathologic conditions causing a similar increase in the sedimentation rate can be excluded.

4. Of the patients having manifest active tuberculosis, 7.35 per cent showed normal sedimentation curves. This group included fourteen cases of minimal, fifty-four of moderately advanced and thirteen of far advanced pulmonary tuberculosis and forty-seven of extrapulmonary tuberculosis.

5. If this working error is discounted, the test gives valuable information concerning the activity of the disease, the amount of tissue destruction and the toxicity of the process. Retarding of the sedimentation speed in a patient in whom it was originally very rapid may be interpreted as a sign of improvement. A constantly increased rate indicates the spread of the disease or the onset of some complication.

6. The test cannot be used for estimating the extent of the lesion. A limited process with marked tissue disintegration and characteristic toxic symptoms will cause a more rapid sedimentation rate than an extensive fibrotic lesion with slight toxicity.

7. A rapid rate found on repeated examinations means an unfavorable prognosis.

8. The greatest merit of the test lies in its value as an index of changes in the general and local condition of the patient. It should be used as a guide for prescribing and controlling routine or special treatment of the tuberculous. It may serve as a valuable aid in connection with the physical examination for determining the patient's working capacity before discharge from the sanatorium and at each reexamination at the dispensary.

THE ACTION AND EXCRETION OF NITRATES*

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Nitrates have long been recognized as effective diuretics. Thomas Willis,[1] in 1679, used potassium nitrate or "the salt of niter" in the treatment of dropsy. Jörg,[2] in 1825, administered increasing doses of potassium nitrate to a normal man and noted its diuretic effect. Wood,[3] in 1856, confirmed the therapeutic action of nitrates, emphasizing the fact that an adequate dose was important in order to produce effective diuresis. Wilks and Taylor,[4] in 1863, gave as much as 18 Gm. of potassium nitrate a day to a patient with renal dropsy, obtaining satisfactory results. About twenty-five years ago the toxicity of nitrates became a practical problem because of the rather extensive use of bismuth subnitrate in diagnostic roentgen procedures. Cases presenting methemoglobinemia were reported[5] and consequently the possible toxic action of nitrates was overemphasized, with the resultant use of small and inadequate doses.

Our previous experiments[6] and those of Gamble[7] showed that certain ammonium salts, including ammonium chloride and ammonium sulphate, were helpful diuretics. It seemed advantageous to give ammonium nitrate a trial, thus combining the effects of an ammonium salt and the well recognized diuretic action of the nitrate ion. Jacobs

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and Keith,[8] in 1926, gave ammonium nitrate to animals and to patients and found that patients could tolerate 10 Gm. daily without toxic effects, and that nausea was a much less troublesome symptom than with other ammonium salts. Since then,[9] we have administered ammonium nitrate in many cases of edema caused by distinctly different pathologic conditions, and usually have obtained satisfactory diuresis without toxic effects. Further experimental work was undertaken to determine the specific effects of nitrates and their site of action. Cahn,[10] in 1886, reported that the concentration of urinary chlorides was increased in the dog after the ingestion of potassium nitrate. Since then it has been frequently confirmed that nitrates produce an increased excretion of chlorides in the urine. The lack of a simple, satisfactory method for the determination of nitrates in body fluids has limited experimental progress in this subject. This difficulty was overcome in the course of the present work by the development of a simple method by one of us (Whelan[11]). We then proceeded to study the effects, under carefully controlled conditions, of the administration of nitrate on the normal dog, on normal persons and on patients with edema. The present communication gives the results of these studies of the action and excretion of nitrates.

EXPERIMENTS ON THE DOG

Method of Study.—Experiments over short periods of time were carried out on six dogs. Female dogs were used because of the ease of obtaining specimens of urine by catheter. Food or water was not given during the control periods or after intravenous injection of the solution of nitrate. A solution of ammonium nitrate, 10 per cent, was injected intravenously at a maximal rate of 2 cc. (0.2 Gm.) each minute and in the amount of from 0.13 to 0.14 Gm. for each kilogram of body weight. Samples of blood were obtained periodically and the concentration of nitrate nitrogen, ammonia nitrogen and urea nitrogen, and the carbon dioxide combining power of the plasma were determined. At stated intervals, the volume, specific gravity, and hydrogen ion concentration of the urine were measured, and estimations were made of the excretion of nitrate, urea, ammonia nitrogen and chloride.[12] When we were studying the combined effects of nitrate and of organic compounds of mercury, a solution of merbaphen, 10 per cent, was injected intravenously in amounts of from 0.037 to 0.04 cc. for each kilogram of body weight. Results in three of these experiments are given in tables 1, 2 and 3.

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12. The chloride has been expressed as chlorine and not as sodium chloride.

Action of Ammonium Nitrate in the Normal Dog.—Studies of the blood in these experiments showed that its content of nitrate nitrogen immediately after injection was high, and that this fell gradually in the next eighteen to twenty-four hours. It is of interest to point out this comparatively slow fall of the anion, or nitrate component, compared with the rapid or almost instantaneous disappearance of the chloride ion after ammonium chloride had been administered. The concentration of ammonia nitrogen (table 1) never was very high, but it fell rapidly and reached the normal level in half an hour to one hour after the injection. The concentration of urea nitrogen in the blood was definitely increased in the course of the first two to four hours. This rapid decrease in ammonia and increase in urea of the blood confirms our previous experiences with ammonium chloride.[6] It indicates that conversion to urea of the ammonia of an ammonium salt occurs soon after the salt enters the blood stream. In a single experiment there occurred a slight fall in the carbon dioxide combining power of the plasma. In further experiments there has been repeatedly a consistent fall of from 10 to 15 per cent by volume.

The volume of urine usually was increased over that of the control period, and in one experiment the amount was actually doubled.[13] The hydrogen ion concentration and the concentration of chloride increased, as did the concentration of ammonia nitrogen. One of us (Whelan) has obtained similar diuresis and response in excretion of chloride in dogs which were given a solution of nitric acid.[14] The amount of urea nitrogen excreted in the first four hours approximated that excreted during the previous control period in two experiments, but in a third experiment the amount was increased. The nitrate nitrogen was excreted in considerable amounts; from 47 to 57.7 per cent of the amount injected was recovered in the urine in from eighteen to twenty-four hours. The highest concentration reached 0.29 Gm. in each 100 cc. of urine (table 2). These urinary phenomena were similar to those previously observed with ammonium chloride in the dog.[6] The increase in the volume of urine and content of the chloride was more frequent after the nitrate than after the chloride. It is significant that some nitrates can cause the output of more chloride in the urine than can some chlorides.

Two experiments, one of which is illustrated in table 3, demonstrate how much more effective is the organic compound of mercury, merbaphen, when it is combined with ammonium nitrate. The combined action results in the excretion of approximately twice the amount of water and chloride in a period of twenty hours (fig. 1).

13. The fact that diuresis did not always occur is evidence that the intravenous injection of the small amount of water in which the salt was dissolved did not have a diuretic effect of itself.

14. Whelan, Mary: Unpublished data.

TABLE 1.—*Action of Ammonium Nitrate in the Normal Dog*

Date	Time	Blood: Whole Blood: Ammonia Nitrogen, Mg. for Each 100 Cc.	Blood: Whole Blood: Urea Nitrogen, Mg. for Each 100 Cc.	Blood: Plasma: Carbon Dioxide Combining Power, per Cent by Volume	Urine: Time of Excretion: Hours	Urine: Time of Excretion: Minutes	Urine: Volume, Cc.	Urine: p_H	Urine: Urea Nitrogen, Gm. for Each 100 Cc.	Urine: Ammonia Nitrogen, Gm. for Each 100 Cc.	Urine: Chloride, Gm. for Each 100 Cc.	Comment
					Dog 1, Female, Weight 10 Kg.							
7/10/28	.....	....	....	..	..	..	....	...	....	....	....	No food or water
7/11/28	10:14 a. m.	0.09	18.7	..	2	..	10.0	...	3.45	0.07	0.12	
	10:18 a. m.	....	....	..	..	..	....	...	....	....	....	Intravenous injection 13.45 cc. (1.34 Gm.) 10 per cent ammonium nitrate solution begun
	10:25 a. m.	....	....	..	..	..	....	...	....	....	....	Intravenous injection finished
	10:27 a. m.	0.39	18.7	..	..	..	....	...	....	....	....	
	10:37 a. m.	0.10	21.5	..	..	19	0.5	...	....	....	....	
	10:52 a. m.	0.08	22.9	..	..	15	2.0	...	2.23	0.07	0.32	
	11:10 a. m.	0.06	18.7	..	..	18	2.0	...	1.95	0.32	0.40	
	11:25 a. m.	0.06	21.0	..	..	15	1.5	...	1.13	0.10	0.46	
	12:25 p. m.	....	18.7	..	1	..	6.5	...	3.06	0.09	0.34	
	2:25 p. m.	....	21.0	..	2	..	13.0	...	3.51	0.13	0.14	Catheter retained in bladder since 10:14 a. m.; urine excretion in four hours 25.5 cc., a slight increase
7/12/28	10:30 a. m.	....	12.0	..	20	..	52.0	...	2.15	0.19	0.19	Urine collected beneath cage
	.....	....	....	..	..	..	23.0	...	2.72	0.24	0.13	Urine collected by catheter
					Dog 2, Female, Weight 12.1 Kg.							
7/16/28	.....	....	....	..	..	..	....	...	....	....	....	1000 cc. water; no food
7/17/28	10:10 a. m.	0.08	14.0	46	2	..	19.0	6.4	2.24	0.02	0.15	
	10:12 a. m.	....	....	..	..	..	....	...	....	....	....	Intravenous injection 17.32 cc. (1.73 Gm.) 10 per cent ammonium nitrate begun
	10:20 a. m.	....	....	..	..	..	....	...	....	....	....	Intravenous injection finished
	10:21 a. m.	0.25	14.5	..	..	..	....	...	....	....	....	
	10:23 a. m.	....	....	..	..	11	16.0	6.4	1.46	0.06	0.31	
	10:50 a. m.	0 10	16.3	..	..	..	....	...	....	....	....	
	11:20 a. m.	0.08	14.5	..	1	..	10.0	5.2	1.64	0.09	0.46	
	12:20 p. m.	....	19.3	41	1	..	10.0	5.0	2.23	0.12	0.31	
	2:20 p. m.	....	14.0	44	2	..	26.0	5.0	2.33	0.17	0.22	Catheter retained in bladder since 10:10 a. m.; urine excreted in four hours, ten minutes, 62 cc., a definite increase

TABLE 2.——*Nitrate Excretion in the Dog (Dog 5, Female, Weight 9.44 Kg.)*

Date	Time	Nitrate Nitrogen, Mg. for Each 100 Cc. of Plasma	Volume, Cc.	Urine								Comment
				Nitrate Nitrogen		Chloride		Urea Nitrogen		Ammonia Nitrogen		
				Gm. for Each 100 Cc.	Gm. Excreted	Gm. for Each 100 Cc.	Gm. Excreted	Gm. for Each 100 Cc.	Gm. Excreted	Gm. for Each 100 Cc.	Gm. Excreted	
10/5/29	8:20 a. m. to 2:19 p. m.	....	28	trace*	.....	0.23	0.064	2.67	0.75	0.17	0.048	Control six hours
	2:21 p. m.	....	..	.....	.....	....	.....	....	....	....	.....	Intravenous injection 12 cc. 10 per cent solution ammonium nitrate (1.2 Gm. or 0.21 Gm. nitrate nitrogen) begun
	2:33 p. m.	8.1	..	.....	.....	....	.....	....	....	....	.....	Intravenous injection finished
	3:05 p. m.	5.7	..	.....	.....	....	.....	....	....	....	.....	
	3:37 p. m.	4.9	..	.....	.....	....	.....	....	....	....	.....	
	4:35 p. m.	4.0	..	.....	.....	....	.....	....	....	....	.....	
	6:35 p. m.	1.9	..	.....	.....	....	.....	....	....	....	.....	
	8:35 p. m.	1.2	28	0.291	0.081	0.28	0.078	2.56	0.72	0.20	0.056	Volume, chloride, urea and ammonia output equal to that of control period
10/6/29	2:35 a. m.	0.65	13	0.105	0.014	0.12	0.016	2.68	0.35	0.30	0.039	
	8:35 a. m.	0.52	13	0.030	0.004	0.02	0.003	2.96	0.38	0.42	0.054	Total nitrate nitrogen excreted in eighteen hours, 0.099 Gm. (47 per cent of amount injected); no food or water given during experiment

* Very small amount; difficult to estimate.

TABLE 3.—*Effect of Ammonium Nitrate on Diuresis Caused by Organic Compounds of Mercury (Dog 4, Female, Weight 11.2 Kg.)*

Date	Time	Urea Nitrogen, Mg. for Each 100 Cc. Blood	Urine: Time of Excretion, Hr.	Urine: Volume, Cc.	Urine: Specific Gravity	Urine: Chloride Gm. for Each 100 Cc.	Urine: Chloride Gm. Excreted	Comment
8/14/28	.....	....	..	..	.....	....	....	600 cc. water; no food
8/15/28	10:20 a.m.	17.0	..	..	.....	....	....	No water or food during experiment
	12:20 p.m.	....	2	7	1.043	0.18	0.01	Urine obtained by catheter at beginning and end of period
	12:24 p.m.	....	..	..	.....	....	....	Merbaphen, 0.43 cc., injected intravenously
	2:25 p.m.	16.6	2	10	1.039	0.13	0.01	
	4:25 p.m.	12.0	2	35	1.021	0.71	0.25	
	6:25 p.m.	....	2	80	1.008	0.59	0.47	
	8:25 p.m.	10.6	2	70	1.007	0.40	0.28	
8/16/28	8:35 a.m.	11.5	12	48	1.020	0.18	0.09	Urine collected beneath cage
				28	1.034	0.08	0.02	Urine collected by catheter, total volume of urine in twenty hours, 271 cc.
9/27/28	.....	....	..	..	....	....	....	600 cc. water; no food
9/28/28	12:17 p.m.	....	2	11	1.023	0.23	0.25	No water or food during experiment
	12:19-27 p.m.	....	..	..	.....	....	....	1.57 Gm. ammonium nitrate injected in 15.75 cc. 10 per cent solution intravenously
	12:30 p.m.	....	..	..	.....	....	....	Merbaphen, 0.46 cc., injected intravenously
	2:30 p.m.	....	2	38	1.019	0.35	0.13	
	4:30 p.m.	....	2	215	1.008	0.59	1.27	
	6:30 p.m.	....	2	135	1.010	0.58	0.78	
	8:30 p.m.	....	2	58	1.011	0.65	0.38	
9/29/28	8:30 a.m.	....	12	69	1.021	0.15	0.10	Urine collected beneath cage
				13	1.038	0.04	0.005	Urine collected by catheter; total urine volume in twenty hours, 528 cc.

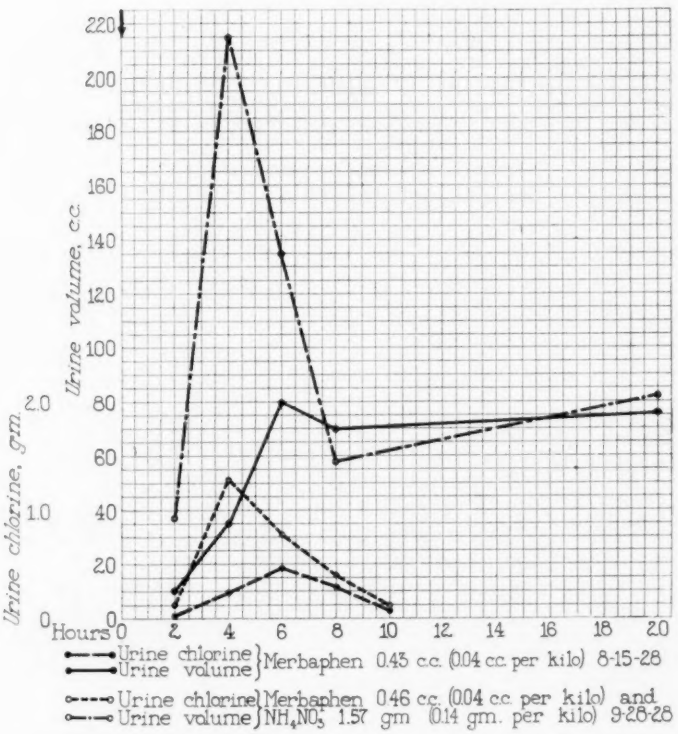
Urine volume, cc.
Urine chlorine, gm.
Hours
Urine chlorine
Urine volume
Merbaphen 0.43 c.c. (0.04 c.c. per kilo) 8-15-28
Urine chlorine
Urine volume
Merbaphen 0.46 c.c. (0.04 c.c. per kilo) and NH4NO3 1.57 gm (0.14 gm. per kilo) 9-28-28

Fig. 1 (dog 4, table 3).—The greater effect of the combined action of merbaphen and ammonium nitrate than merbaphen alone on the renal excretion of water and chloride is shown.

EXPERIMENTS ON NORMAL MEN

Method of Study.—Detailed metabolic studies both before and after the ingestion of nitrates were carried out on four normal young men. In order to have accurate experimental conditions, these subjects were given a constant weighed diet, low in content of mineral salts and of water, but adequate in protein and total calories. Except for variation in vegetables, the same food was given each day. A carefully made record was kept of any food not eaten. In table 4 are given the calculated values of certain of the constituents and the variations of the diet. The additional daily intake of water was measured; it amounted to between 200 and 800 cc., usually from 600 to 800 cc. Daily specimens of urine were collected, and in some cases, daily collections of stools were made also. There was always a preliminary control period of from two to four days, so that the storage of water and salts was at a minimum. The subjects were then given from 8 to 10 Gm. of ammonium nitrate daily, in single or divided doses, over varying periods of time. The ammonium nitrate was given in 25 or 30 per cent solution flavored with peppermint water. To normal man 3, sodium nitrate and ammonium acetate were also administered in solution under conditions similar to those under which ammonium nitrate was given, and in amounts approximately equivalent to those in which ammonium nitrate was given.

TABLE 4.—*Composition of Low Mineral and Low Water Diets in Grams*

Type	Carbohydrates	Protein	Fat	Calories	Water	Sodium	Potassium	Calcium	Magnesium	Chloride	Phosphorus	Sulphur	Iron
1	175	50	126	2,095	872	0.75	1.77	0.29	0.21	0.87	0.74	0.69	0.011
2	230	59	93	2,050	890	0.70	2.29	0.35	0.21	0.86	0.87	0.80	0.013
3	240	50	144	2,530	895	0.77	1.87	0.31	0.22	0.89	0.75	0.70	0.011
4	300	60	110	2,500	895	0.70	2.21	0.27	0.22	0.87	0.87	0.80	0.013

We have considered the quantitative development of color with the diphenylbenzidene reagent in the urine and body fluids after the ingestion of nitrates as being due to nitrates. It could be due to nitrites, as has been pointed out by one of us (Whelan), but if such large amounts had been present, as would be indicated by the changes in color that have taken place, very toxic symptoms would have developed. Further chemical studies are being carried out in order to estimate separately the concentration of nitrate and nitrite in a given body fluid.[15]

In these subjects, samples of blood were taken periodically before breakfast. The concentration in the whole blood of various constituents was determined. Haden's method[16] for the determination of hemoglobin was used, except that the color was developed according to the method devised by Osgood and Haskins.[17]

15. Several substances that are normally present and others that might possibly be found in body fluids in these subjects and in cases of edema were tested with the nitrate reagent. The color reaction did not develop with solutions of the following substances: dextrose, skatol, glycuronic acid (borenol glycuronic acid), diabetic urine, phenobarbital, acetylsalicylic acid, theophylline-ethylenediamine and the organic mercury compounds, merbaphen and mersalyl (salyrgan).

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17. Osgood, E. E., and Haskins, H. D.: A Permanent Standard for the Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

In determining nonprotein nitrogen, the methods of Folin and Denis [18] were employed. Urea nitrogen was determined by van Slyke and Cullen's [19] modification of Marshall's method, and ammonia nitrogen by the method of Nash and Benedict.[20] Cholesterol was determined by the method of Bloor and Knudson; [21] creatinine by the method of Folin and Wu; [22] proteins of the serum or plasma by the method of Howe,[23] and plasma chlorides were determined according to the technic of Osterberg and Schmidt [24] with slight modifications; the technic is the same except that 9 cc. of the dilute nitric acid is added to 1 cc. of serum or plasma followed by 2 cc. of silver nitrate (1 cc. of which is equivalent to 4 mg. of sodium chloride) and centrifugated. An aliquot part or 10 cc. of this is titrated with ammonium thiocyanate. The determination of base was carried out according to the method of Stadie and Ross.[25] Bicarbonate was determined by the method of van Slyke and Cullen,[26] and of van Slyke and Stadie.[27] The nitrate nitrogen was estimated by the method of Whelan.[11] The carbon dioxide combining power of the serum was determined by the procedure of van Slyke and Cullen.[26] Calcium was determined by the method of Clark and Collip [28] which is a modification of the method of Kramer and Tisdall.[29] The method of Kramer and Tisdall [29] was used for precipitation of the magnesium as magnesium ammonium phosphate. The phosphorus in the precipitate was determined by the method of Fiske and Subbarow.[30] Sulphates were determined by a method

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27. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1 (Nov.) 1921.

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29. Kramer, Benjamin, and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921.

30. Fiske, C. H., and Subbarow, Yellapragada: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

devised by Wakefield and Power.[31] The protein content of serum was estimated from its content of nitrogen as determined by the Kjeldahl method. The content of water was determined by drying a known amount of serum to a constant weight. Potassium and sodium were determined by the methods of Kramer and Tisdall,[32] except that certain modifications of their method for determination of sodium were made.

The specific gravity of the urine was recorded and the hydrogen ion concentration was determined by the method of Gillespie.[33] The total acidity was determined by the method of Folin.[34] Other constituents studied were as follows: the chloride in the urine that did not contain protein by the method of Volhard and Harvey;[35] the chloride in the urine that contained protein by Wilson and Ball's method[36] for blood chlorides, the phosphorus by the method of Fiske and Subbarow,[30] and the sulphate by the method of Folin.[37] When protein nitrogen was present in the urine (as in the cases of edema that are to be presented) it was determined by getting the difference between the total nitrogen and the non-protein nitrogen. The method of Folin and Denis[38] was used. The protein was precipitated by acid tungstate. Urea nitrogen was estimated by the same method used in estimating it in the blood. Creatinine nitrogen was determined by the method of Folin.[39] Ammonium nitrogen was determined by the usual aeration method. Nitrate nitrogen was determined by the method devised by Whelan[11] not only in the blood and the urine but also in saliva and edema fluid.

In normal man 4, a study was made of the combined action of nitrate and the organic compound of mercury, mersalyl. A 10 per cent solution of this substance was injected intravenously in doses of 1 cc. The total amount of nitrogen in the stools was determined by the Kjeldahl method in the cases in which studies of nitrogen balance were carried out. In certain persons, the amount of nitrate nitrogen in the stools also was determined by the modified Divarda method, since our colorimetric method was unsatisfactory when it was applied to the specimens of stool. In order to determine the nitrogen balance in persons who were taking nitrate, it was necessary to estimate the concentration of nitrate nitrogen in the urine and feces, since nitrates are broken down and pass off during the usual

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Kjeldahl digestion. Thus, we were able to carry out separate estimations of the usual nitrogenous constituents of the urine and stool, and of the nitrates. In consequence, it is possible to distinguish between changes in metabolism of nitrate and the effects of the nitrate on the general metabolism of the body, especially that of protein and of nitrogen. In the present study, the term nitrogen balance is used in the latter sense.[40]

ACTION OF AMMONIUM NITRATE AND OF SODIUM NITRATE

Studies of the blood of normal persons showed that the concentration of nitrate nitrogen of the plasma rose to between 2 and 3 mg. in each 100 cc., during the administration of the nitrate, but that after its withdrawal, the concentration fell rapidly in forty-eight hours. In a single experiment the ammonia nitrogen rose slightly to 0.16 mg. in each 100 cc., confirming the rapid disappearance observed in the dog. There were no marked or constant shifts in the concentration of hemoglobin. The concentration of urea nitrogen usually did not change, but in one experiment it rose slightly, as did the total nonprotein nitrogen. The concentration of the nonprotein nitrogen decreased in two instances. The concentration of chloride in the plasma did not vary consistently, nor was there consistent change in the carbon dioxide combining power. The latter phenomenon was in distinct contrast to the fall in carbon dioxide combining power seen after the ingestion of similar amounts of ammonium chloride, as noted by Haldane,[41] Keith, Barrier and Whelan,[6] Gamble, Blackfan and Hamilton[7] and Folling.[42]

The effects of ammonium nitrate on urinary excretion were surprisingly similar in the first three normal subjects represented in tables 5, 6 and 7. The increase in volume of the urine, hydrogen ion concentration, concentration of chloride, total fixed base, nitrate nitrogen, total nitrogen, urea nitrogen and ammonia nitrogen were definite and sometimes marked. There was frequently a small increase in inorganic sulphates, inorganic phosphates and titratable acidity. It is evident that the increased excretion of certain of these substances was due to the ingested nitrate because of the marked decrease in output during the second control period. During the second control period the volume of urine and the concentration of many of the urinary constituents were actually less than during the initial control days. This indicates that the tissues had been deprived of these substances and of water in considerable amounts and tended to retain what remained. This was particularly noticeable in regard to water, chloride and total fixed base (table 5).

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40. The total nitrogen balance, including the nitrate, can be calculated readily from the tables.

41. Haldane, J. B. S.: Experiments on the Regulation of the Blood's Alkalinity, J. Physiol. **55**:265 (Aug.) 1921.

42. Folling, A.: On the Mechanism of the Ammonium Chloride Acidosis, Acta med. Scandinav. **71**:221, 1929.

TABLE 5.—*Daily Average of Urine and Total Nitrogen Balance*

	Age, Years	Sex	Body Weight, Kg.	Volume of Urine, Cc.	p_H	Chloride, Gm.	Total Fixed Base, Cc. of 0.1 Normal	Non-protein Nitrogen, Gm.	Protein Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.	Nitrogen Balance, Gm.	Nitrate Nitrogen Balance, Gm.
Normal man 1	30	M												
First control period	..	..	57.7	850	6.0	0.80	998	8.24	....	6.38	0.39	....	.....	.....
Nitrate period*	..	..	56.3	1,030	5.6	1.19	1,375	10.39	....	8.00	0.93	....	.....	.....
Second control period	..	..	56.8	785	6.2	0.16	248	8.67	....	6.56	0.78	....	.....	.....
Normal man 2	34	M												
First control period	..	..	72.6	695	5.5	0.69	541	7.32	....	5.76	0.67	0.48	—0.1	.....
Nitrate period	..	..	69.9	990	4.9	1.43	1,043	9.38	....	7.28	1.37	0.51	—0.1	.....
Second control period	..	..	69.2	580	5.4	0.12	284	7.51	....	6.64	0.52	0.46	—0.1	.....
Normal man 3	28	M												
First control period	..	..	75.8	810	6.2	1.19	1,007	11.09	....	7.88	0.42	0.68	—2.1	.....
Nitrate period	..	..	74.3	1,000	5.4	1.44	1,399	12.4	....	9.84	1.15	0.77	—0.6	+0.36
Second control period	..	..	75.1	520	5.9	0.33	414	8.9	....	7.37	0.86	0.70	—0.3	—0.14
Normal man 3 (sodium nitrate)														
First control period	..	..	75.3	810	6.0	1.34	1,036	9.10	....	7.52	0.39	0.69	0	.....
Nitrate period	..	..	74.6	895	5.8	1.12	1,657	8.96	....	7.41	0.30	0.73	—0.6	+0.41
Second control period	..	..	74.6	750	6.2	0.38	690	6.00	....	4.52	0.21	0.48	.....	—0.35
Normal man 3 (ammonium acetate)														
First control period	..	..	77.0	680	5.8	1.53	1,000	8.75	....	6.59	0.26	0.73	+0.1	.....
Nitrate period	..	..	76.1	475	5.6	0.33	710	10.66	....	8.96	0.41	0.74	—0.2	.....
Second control period	..	..	76.0	475	5.6	0.33	640	10.50	....	8.93	0.42	0.74	.....	.....
Chronic glomerulonephritis with edema (case 1)	40	F												
First control period	..	..	62.9	745	6.2	0.98	.....	5.53	1.58	3.65	0.56	0.40	0	.....
Nitrate period	..	..	61.8	1,330	5.2	2.49	.....	5.14	1.15	3.65	0.62	0.43	+2.0	.....
Second control period	..	..	60.0	1,060	6.6	0.98	.....	4.24	1.18	3.05	0.37	0.38	+0.8	.....
Chronic glomerulonephritis with edema (case 2)	30	M												
First control period	..	..	94.1	525	6.2	1.53	996	6.11	2.66	4.85	0.34	0.57	—2.0	.....
Nitrate period	..	..	87.8	745	5.9	2.03	1,277	5.99	2.32	4.51	0.57	0.54	—1.2	.....
Second control period	..	..	78.0	1,130	6.8	4.75	2,221	5.64	2.83	4.20	0.42	0.51	—2.2	.....
Chronic nephrosis (case 3)	15	F												
Control period	..	..	57.3	875	...	.....	.....	3.08	0.62	....	....	....	+3.3	.....
Nitrate period	..	..	53.5	1,250	...	.....	.....	5.93	1.24	....	....	....	.....	+0.38
Chronic glomerulonephritis with edema (case 4)	24	F												
Control period	..	..	78.6	1,325	5.6	2.72	1,590	3.80	2.93	2.31	0.32	0.27	+2.1	.....
Nitrate period	..	..	74.5	1,840	5.3	4.66	2,219	5.47	3.30	3.74	0.31	0.265	+1.9	+1.02
Chronic nephrosis (case 5)	24	M												
First control period	..	..	72.7	595	5.6	0.52	599	9.30	1.91	8.02	0.36	0.59	—2.9	.....
Nitrate period	..	..	69.1	935	5.5	2.97	1,386	10.90	1.09	9.07	0.65	0.52	—2.0	+0.43
Second control period	..	..	70.0	595	5.7	0.31	292	8.64	0.91	6.77	0.95	0.50	—1.6	—0.28
Chronic nephrosis (case 6)	47	M												
First control period	..	..	72.6	600	5.8	2.09	.....	.....	....	....	....	....	.....	.....
Nitrate period	..	..	66.4	1,105	5.4	3.07	.....	.....	....	....	....	....	.....	.....
Second control period	..	..	65.8	550	5.4	1.60	.....	.....	....	....	....	....	.....	.....

* Ammonium nitrate given unless otherwise stated.

TABLE 6.—*Nitrogen Metabolism (Normal Man 3)*

Date, 1928	Body Weight, kg.	Nitrogen Intake			Blood*			Urine					Feces, Total Nitrogen, Gm.	Feces and Urine, Total Nitrogen, Gm.	Comment
		Total, Gm.	Food, Gm.	Ammonia, Gm.	Non-protein Nitrogen, Mg. for Each 100 Cc.	Urea Nitrogen, Mg. for Each 100 Cc.	Nitrate Nitrogen, Mg. for Each 100 Cc.	Volume, Cc.	Total Non-protein Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.			
2/18	77.3	...	...	....	..	..	....	.....	.....	.....	....	....	....	.....	
2/18-19	76.7	9.6	9.6	....	..	..	....	900	10.35	6.95	0.51	0.67	0.51	10.86	
2/19-20	76.4	9.6	9.6	....	..	..	....	850	11.20	7.50	0.36	0.63	....	11.20	
2/20-21	76.0	9.6	9.6	....	..	..	....	850	12.90	9.50	0.48	0.69	2.13	15.03	
2/21-22	75.8	9.6	9.6	....	35	15	0.06	650	9.90	7.55	0.33	0.73	....	9.90	Nitrogen balance (4 days), daily average —2.1 Gm.
2/22-23	75.8	11.35	9.6	1.75	..	..	....	825	11.00	8.70	0.74	0.68	2.34	13.34	10 Gm. ammonium nitrate given†
2/23-24	74.8	11.35	9.6	1.75	..	..	....	950	11.2	9.70	1.11	0.78	....	11.20	10 Gm. ammonium nitrate given
2/24-25	74.3	11.35	9.6	1.75	..	..	....	1,175	14.7	11.25	1.31	0.84	2.95	17.65	10 Gm. ammonium nitrate given
2/25-26	74.3	11.35	9.6	1.75	..	..	2.8	1,050	12.8	9.70	1.47	0.78	....	12.80	10 Gm. ammonium nitrate given, total 40 Gm.; nitrogen balance (4 days), daily average —0.6 Gm.
2/26-27	74.8	9.6	9.6	....	30	15	3.1	450	8.7	6.56	1.26	0.75	1.85	10.55	
2/27-28	75.0	9.6	9.6	....	..	..	1.2	650	8.6	6.95	0.75	0.65	....	8.60	
2/28-3/1	75.1	9.6	9.6	....	..	..	0.2	425	8.6	7.45	0.73	0.70	....	8.60	
3/ 1-2	75.1	9.6	9.6	....	..	..	0.01	550	9.7	8.54	0.69	0.74	2.20	11.90	Nitrogen balance (4 days), daily average —0.3 Gm.

* Blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

TABLE 7.—*Mineral Metabolism (Normal Man 3)*

Date, 1928	Nitrate Nitrogen Intake, Gm.	Blood* Plasma Hemoglobin, Gm. for Each 100 Cc.	Blood* Plasma Chloride, Gm. for Each 100 Cc.	Blood* Plasma Nitrate Nitrogen, Mg. for Each 100 Cc.	Blood* Plasma Carbon Dioxide Combining Power, per Cent by Volume	Urine Volume, Cc.	Urine *p*H	Urine Chloride Gm.	Urine Chloride Cc. N/10	Urine Phosphorus Gm.	Urine Phosphorus Cc. N/10	Urine Sulphate as Sulphur Trioxide Gm.	Urine Sulphate as Sulphur Trioxide Cc. N/10	Urine Nitrate Nitrogen Gm.	Urine Nitrate Nitrogen Cc. N/10	Urine Nitrate Nitrogen Balance, Gm.	Urine Titratable Acidity, Cc. N/10	Urine Total Fixed Base, Cc. N/10	Urine Ammonia Nitrogen Gm.	Urine Ammonia Nitrogen Cc. N/10	Comment
2/18-19	....	....	...	....	..	900	6.2	2.16	310	0.51	166	1.46	365	0.001	1.3	.....	222	1,119	0.51	360	
2/19-20	....	....	...	....	..	850	5.8	1.62	455	0.63	204	1.47	368	0.003	1.9	.....	278	976	0.36	262	
2/20-21	....	....	...	....	..	850	6.4	1.19	336	0.77	249	1.56	390	0.002	1.2	.....	204	1,040	0.48	340	
2/21-22	....	17	345	0.06	58	650	5.8	0.78	210	0.60	194	1.53	383	0.000	0.3	.....	192	794	0.33	245	
2/22-23	1.75	....	...	...	..	825	5.6	1.49	420	0.69	224	1.36	340	1.01	722	+0.64	279	1,340	0.74	525	10 Gm. ammonium nitrate†
2/23-24	1.75	....	...	....	..	950	5.4	1.61	455	0.84	270	1.62	405	1.48	1,055	+0.27	274	1,567	1.11	793	10 Gm. ammonium nitrate given
2/24-25	1.75	....	...	2.8	..	1,175	5.2	1.53	430	1.04	334	1.80	450	1.42	1,015	+0.33	330	1,540	1.31	935	10 Gm. ammonium nitrate given
2/25-26	1.75	17.8	405	3.1	56	1,050	5.2	1.15	324	0.93	298	1.78	445	1.65	1,180	+0.10	252	1,150	1.47	1,050	10 Gm. ammonium nitrate given, total 40 Gm.
2/26-27	....	....	385	1.2	..	450	5.8	0.54	152	0.78	250	1.49	373	0.37	262	−0.37	198	460	1.26	900	
2/27-28	....	....	...	0.2	..	650	6.0	0.31	88	0.53	170	1.40	350	0.16	116	−0.16	161	399	0.76	543	
2/28-3/1	....	....	...	0.01	..	425	5.8	0.21	59	0.61	196	1.58	395	0.04	31	−0.04	174	348	0.73	520	
3/1-2	....	....	...	....	..	550	6.0	0.26	73	0.62	198	1.47	366	0.006	4.3	−0.01	185	450	0.69	493	

* Blood taken at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

The excretion of nitrate was determined in normal man 3 (table 7) after the ingestion of ammonium nitrate. The concentration of nitrate nitrogen in the urine varied from 0.01 to 0.15 Gm. in each 100 cc. Seventy-nine per cent of the nitrate ingested was excreted during the period of intake, whereas up to 88 per cent was recovered if the concentration of nitrate in the urine was estimated during the subsequent three to four days. The curve of excretion and the total amount eliminated were essentially the same whether the drug was given as ammonium nitrate or as sodium nitrate (tables 8 and 9 and fig. 2).

The increased excretion of total nitrogen after ammonium nitrate had been given was accompanied by increases in inorganic sulphate and in the urea and ammonia and in one experiment (normal man 3, table 6) in the creatinine fraction. The ratio of inorganic sulphate to total nitrogen in the urine tends to be constant. The excretion of urea nitrogen increased from 1.5 to 2.3 Gm. a day and the total nitrogen from 1.3 to 2.1 Gm. in the different experiments. This increase in urea can be wholly explained by the conversion of the ingested ammonia of the ammonium nitrate to urea. Liberation of urea from the tissues, due to changes in metabolism of water and of minerals, is also a possible source of this increase in the excretion of nitrogen and of urea, but the experiments on nitrogen balance suggest that if the increase is due to these changes, it is of less significance. The increase in ammonia nitrogen appears to be a part of the attempt of the tissues to neutralize the action of the nitrate anion. This increase in ammonia often is prolonged after the ingestion of nitrate has been discontinued, an observation noted by Folling after administration of ammonium chloride. This fact suggests that when retention of salts, including chloride and fixed base, takes place, ammonia remains the chief factor in neutralization and continues to be excreted.

Experiments on nitrogen balance have been carried out in animals by Grafe,[43] Grafe and Wintz,[44] and Abderhalden and Hirsch,[45] and sodium nitrate has been shown to cause retention of nitrogen, even when the nitrate is quantitatively excreted. It should be stated that the methods for quantitative estimation of nitrate used in their experiments were not found to be accurate in our hands. Grafe and Wintz also

43. Grafe, E.: Zur Frage der Eiweissynthese bei Fütterung von Ammoniaksalzen, Verhandl. d. Kong. f. inn. Med. **29**:507, 1912.

44. Grafe, E., and Wintz, H.: Ueber die Beeinflussung des Stickstoff-Stoffwechsels durch Fütterung von Natriumnitrat, Ztschr. f. physiol. Chem. **86**:283 (July) 1913.

45. Abderhalden, Emil; and Hirsch, Paul: Weiterer Beitrag zur Kenntnis der synthetischen Fähigkeiten der tierischen Zelle. Die Wirkung des Salpeters (Natrium-nitrats) auf den Stickstoffstoffwechsel, Ztschr. f. physiol. Chem. **84**: 189 (April) 1913.

TABLE 8.—*Nitrogen Metabolism (Normal Man 3)*

Date, 1928	Body Weight, Kg.	Nitrogen Intake		Blood*			Urine					Feces, Total Nitrogen, Gm.	Feces and Urine, Total Nitrogen, Gm.	Comment
		Total, Gm.	Food, Gm.	Non-protein Nitrogen, Mg. for Each 100 Cc.	Urea Nitrogen, Mg. for Each 100 Cc.	Nitrate Nitrogen, Mg. for Each 100 Cc.	Volume, Cc.	Total Non-protein Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.			
3/18	76.1	...	...	....	....	....	.....	....	....	. ..	....	....	.....	
3/18-19	75.7	...	9.6	....	....	....	775	6.70	5.52	0.33	0.62	....	6.70	
3/19-20	75.3	...	9.6	....	....	....	900	9.50	7.82	0.42	0.68	2.53	12.03	
3/20-21	75.3	...	9.6	....	....	....	875	10.50	8.70	0.37	0.77	....	10.50	
3/21-22	75.3	...	9.6	38	12.6	Trace	700	9.80	8.05	0.43	0.71	....	9.80	Nitrogen balance (four days) 0
3/22-23	75.1	9.6	9.6	....	....	2.08	700	8.95	7.35	0.39	0.71	2.45	11.40	10 Gm. sodium nitrate given†
3/23-24	74.6	9.6	9.6	....	....	1.88	1,100	9.90	8.05	0.22	0.75	....	9.90	10 Gm. sodium nitrate given
3/24-25	74.6	9.6	9.6	....	12.6	2.44	900	8.69	7.13	0.25	0.73	....	8.60	10 Gm. sodium nitrate given
3/25-26	74.6	9.6	9.6	31.4	12.2	2.64	875	8.40	7.10	0.32	0.73	2.34	10.74	10 Gm. sodium nitrate given, total 40 Gm., nitrogen balance (4 days), daily average −0.6 Gm.
3/26-27	74.6	9.6	9.6	....	....	1.06	750	6.00	4.52	0.21	0.49	....	6.35	

* Specimen of the blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

TABLE 9.—*Mineral Metabolism (Normal Man 3)*

Date, 1928	Nitrate Nitrogen Intake, Gm.	Blood: Plasma: Hemoglobin, Gm. for Each 100 Cc.	Blood: Plasma: Chloride, Gm. per Cent	Blood: Plasma: Carbon Dioxide Combining Power, per Cent by Volume	Urine: Volume, Cc.	Urine: p_H	Urine: Chloride Gm.	Urine: Chloride Cc. N/10	Urine: Phosphorus Gm.	Urine: Phosphorus Cc. N/10	Urine: Sulphate as Sulphur Trioxide Gm.	Urine: Sulphate as Sulphur Trioxide Cc. N/10	Urine: Nitrate Nitrogen Gm.	Urine: Nitrate Nitrogen Cc. N/10	Urine: Nitrate Nitrogen Balance, Gm.	Urine: Titratable Acidity, Cc. N/10	Urine: Total Fixed Base, Cc. N/10	Urine: Ammonia Nitrogen Gm.	Urine: Ammonia Nitrogen Cc. N/10	Comment
3/18-19	....	....	...	..	775	6.8	2.32	654	0.57	187	1.15	288	....	...	.....	121	1,255	0.33	233	
3/19-20	....	....	...	..	900	6.2	1.26	255	0.70	226	1.52	380	....	...	.....	245	1,040	0.42	302	
3/20-21	....	....	...	..	875	6.2	0.88	248	0.98	316	1.61	402	....	..	.....	235	930	0.37	263	
3/21-22	....	15.7	382	74	700	6.0	0.91	256	0.64	206	1.46	365	....	...	.....	185	820	0.43	307	
3/22-23	1.65	....	...	..	700	5.8	0.98	276	0.73	234	1.43	358	0.97	683	+0.68	224	1,325	0.39	280	10 Gm. sodium nitrate given*
3/23-24	1.65	....	...	..	1,100	6.0	1.65	465	0.65	210	1.39	348	1.39	994	+0.26	158	1,970	0.22	157	10 Gm. sodium nitrate given
3/24-25	1.65	15.6	400	..	900	5.8	0.81	228	0.69	221	1.48	370	1.29	925	+0.36	195	1,680	0.25	180	10 Gm. sodium nitrate given
3/25-26	1.65	15.6	...	64	875	6.2	1.05	296	0.69	221	1.52	381	1.31	937	+0.34	144	1,655	0.32	231	10 Gm. sodium nitrate given, total 40 Gm.
3/26-27	....	....	364	..	750	6.4	0.38	108	0.42	136	0.83	208	0.35	250	−0.35	86	690	0.21	150	

* Given in 25 per cent solution; diet 4, additional daily water 800 cc.

found that ammonium salts, although they did not include nitrate, gave rise to retention of nitrogen. In the present study, the nitrogen balance was calculated in four experiments, once in normal man 2, and on three occasions in normal man 3 (table 5). Normal man 2 was in nitrogen equilibrium throughout. In the first experiment on normal man 3, during the initial control period, the man was in negative balance. When he was taking ammonium nitrate, the previous negative balance was decreased, and in the second control period this decrease was even

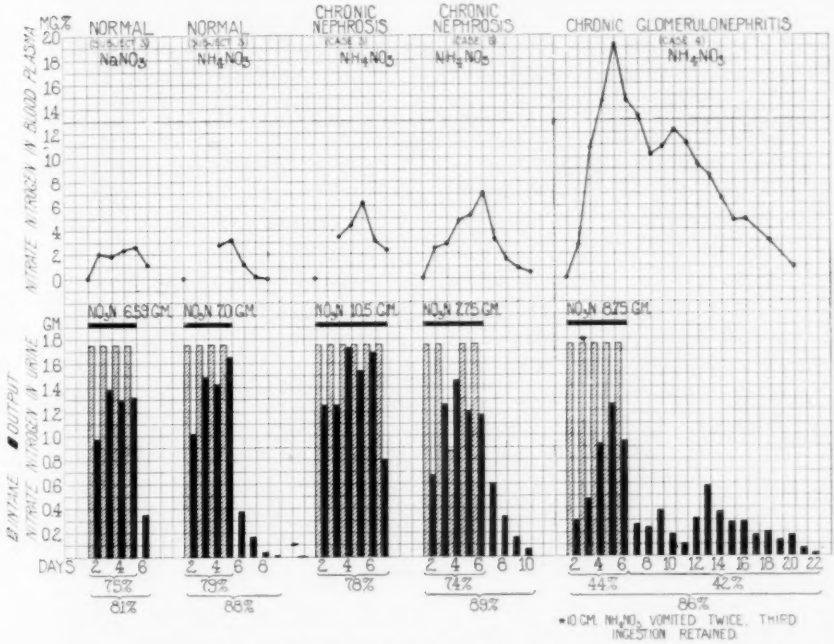

Fig. 2 (normal man 3, and cases 3, 4 and 5).—The effect of sodium nitrate and ammonium nitrate on the nitrate nitrogen of the blood plasma and the excretion of nitrate nitrogen in the urine is shown.

greater, so that a relative positive balance had occurred. In the experiments with sodium nitrate, a slightly negative balance ensued, whereas when ammonium acetate was employed, nitrogen equilibrium was maintained. Thus, in our study the nitrogen balance was variable, and only in a single experiment did retention of nitrogen occur.

The experiments on normal man 3, with sodium nitrate and ammonium acetate, were planned to determine the relative action of these salts in comparison with ammonium nitrate. The effect of sodium nitrate

was definitely less marked than that of ammonium nitrate (tables 8 and 9). The hydrogen ion concentration of the urine and the excretion of ammonia were not increased, which is evidence that there was not a marked disturbance in the acid-base equilibrium. The increase in nitrate and chloride had been met by excess excretion of a fixed base, the source of which most probably was the sodium of the ingested sodium nitrate. The observations in one experiment (tables 10 and 11), after the ingestion of ammonium acetate, are significant. This salt was purposely given to ascertain the effect of the ammonium radical, for the acetate portion of the salt is known to be readily catabolized and rapidly excreted as carbon dioxide and water, the former by way of the lungs, and thus has no appreciable effect on the acid-base equilibrium. This substance had no effect on the hydrogen ion concentration or on the excretion of inorganic salts or water; the latter actually decreased as the experiment progressed. This decrease in the excretion of water and inorganic salts was to be expected because of the very low content of water and salts in the diet. As was anticipated, there was an increased excretion of total nitrogen and urea. The actual increase in ammonia nitrogen was slight. The considerable rise in the concentration of blood urea nitrogen, from 15 to 22 mg. in each 100 cc., probably was partially related to the small output of water in the urine. We reported a like result in a normal man after he had taken ammonium chloride. These results with ammonium acetate suggest that the more marked diuretic effect from ammonium nitrate is not due to the ammonium radical, but to a specific effect of the nitrate. The greater activity of ammonium nitrate, in contrast to sodium nitrate, depends on the difference in the character of the base with which the nitrate ion is combined. The decrease in body weight, especially after administration of ammonium nitrate, appears to be due to the loss of water.

In normal man 4, diuresis occurred on the first day of the control period; that is just after the diet low in salt was instituted. The volume of urine on that day was 2,150 cc., and the excretion of chloride 5.38 Gm. Nonnenbruch [46] has shown that a diet low in salt, similar to that used in this experiment, may cause diuresis in the normal subject. After this diuresis had subsided mersalyl was given, both before and after the ingestion of ammonium nitrate. During the entire experiment, routine examinations of the urine did not reveal any albumin or abnormality in the sediment. The measurable diuretic effect of the two administrations of this drug was approximately the same. However, at the time of the second injection, the store of water and inorganic salts had

46. Nonnenbruch, W.: Ueber Diurese, Ergebn. d. inn. Med. u. Kinderh. **26**: 119, 1924.

TABLE 10.—*Nitrogen Metabolism (Normal Man 3)*

Date, 1928	Body Weight, Kg.	Nitrogen Intake			Blood*		Urine					Feces, Total Nitrogen, Gm.	Feces and Urine, Total Nitrogen, Gm.	Comment
		Total, Gm.	Food, Gm	Ammonia, Gm.	Nonprotein Nitrogen, Mg. for Each 100 Cc.	Urea Nitrogen, Mg. for Each 100 Cc.	Volume, Cc.	Total Nonprotein Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.			
5/20	79.5	.....	...	....	..	..	.....	.....	.....	....	....	....	.....	
5/20-21	78.7	.....	9.6	....	..	..	1,000	8.85	6.4	0.42	0.75	....	8.85	
5/21-22	78.0	.....	9.6	....	..	..	725	9.60	6.45	0.25	0.75	....	9.60	
5/22-23	77.3	.....	9.6	....	..	..	550	8.15	5.90	0.18	0.72	2.78	10.93	
5/23-24	77.0	.....	9.6	....	..	15	450	8.40	7.00	0.21	0.75	....	8.40	Nitrogen balance (4 days), +0.6 Gm.
5/24-25	76.8	11.35	9.6	1.75	..	..	400	9.90	6.80	0.41	0.76	....	9.90	9.62 Gm. ammonium acetate given†
5/25-26	76.1	11.35	9.6	1.75	..	..	475	10.10	8.95	0.49	0.74	1.95	12.05	9.62 Gm. ammonium acetate given
5/26-27	76.4	11.35	9.6	1.75	..	..	525	11.75	10.25	0.39	0.73	....	11.75	9.62 Gm. ammonium acetate given
5/27-28	76.1	11.35	9.6	1.75	33	22	500	10.90	9.85	0.35	0.75	1.74	12.64	9.62 Gm. ammonium acetate given; total 38.5 Gm.; nitrogen balance (4 days), −0.9 Gm.
5/28-29	76.0	.....	9.6	....	..	..	475	10.50	8.93	0.42	0.74	....	10.50	

* Specimen of the blood taken and body weight determined before breakfast at end of twenty-four hour period; diet 4, additional water 800 cc.
† Given in 25 per cent solution.

TABLE 11.—*Mineral Metabolism (Normal Man 3)*

Date, 1929	Blood*			Urine												Comment
		Plasma														
	Hemoglobin, Gm. for Each 100 Cc.	Chloride Gm. for Each 100 Cc.	Carbon Dioxide Combining Power, per Cent by Volume	Volume, Cc.	p_H	Chloride		Phosphorus		Sulphate as Sulphur Trioxide		Titratable Acidity, Cc. N/10	Total Fixed Base, Cc. N/10	Ammonia Nitrogen		
						Gm.	Cc. N/10	Gm.	Cc. N/10	Gm.	Cc. N/10			Gm.	Cc. N/10	
5/20-21	....	...	..	1,000	6.6	3.2	900	0.74	238	1.48	390	152	1,610	0.42	300	
5/21-22	....	...	..	725	6.6	1.38	388	0.60	194	1.18	295	116	1,135	0.25	179	
5/22-23	....	...	..	550	6.2	0.94	265	0.50	161	1.32	330	125	835	0.18	129	
5/23-24	17.1	376	60	450	5.8	0.59	166	0.59	191	1.46	365	194	770	0.21	150	
5/24-25	....	...	..	400	5.6	0.44	124	0.56	181	1.16	290	144	635	0.41	293	9.62 Gm. ammonium acetate given†
5/25-26	....	...	..	475	5.6	0.33	93	0.80	258	1.53	382	247	730	0.49	350	9.62 Gm. ammonium acetate given
5/26-27	....	...	..	525	5.8	0.32	90	0.78	252	1.32	330	220	756	0.39	278	9.62 Gm. ammonium acetate given
5/27-28	17.1	...	61	500	5.6	0.25	71	0.77	248	1.67	417	240	720	0.35	250	9.62 Gm. ammonium acetate given, total 38.5 Gm.
5/28-29	....	...	..	475	5.6	0.33	93	0.72	232	1.53	382	227	640	0.42	300	

* Diet 4, additional water 800 cc.

† Given in 25 per cent solution.

been decidedly depleted so that in reality the diuretic effect of the ammonium nitrate and mersalyl was greater than the latter compound alone (fig. 3). This result is in accord with that obtained in the dog and also with that obtained in previous experiments with ammonium chloride and organic compounds of mercury.

Since inorganic nitrates are diffusible substances, it seemed important to determine their presence, and if they were found in a considerable

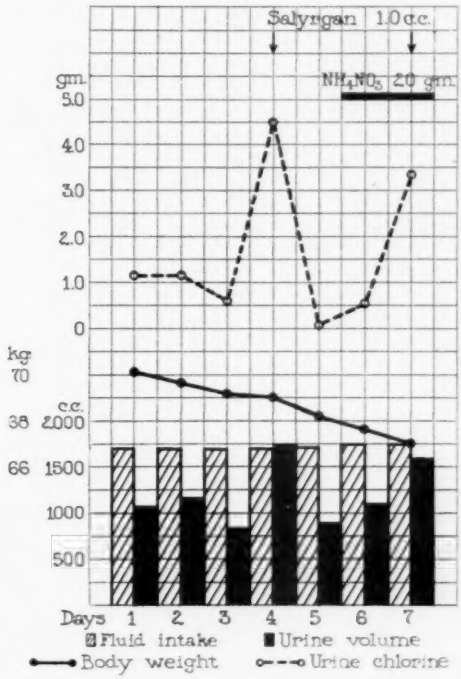

Fig. 3 (normal man 4).—The relatively greater effect of the combined action of mersalyl and ammonium nitrate than mersalyl (salyrgan) alone on the renal excretion of water and chloride is shown.

amount, it seemed advisable to determine their concentration in the saliva of normal persons. The concentration of nitrate nitrogen in the saliva was found to vary from 0.007 to 0.52 mg. in each 100 cc. This great variation in concentration possibly was due to differences in the diet and in the time of collection.

In normal man 2, the concentration of nitrate nitrogen in the feces was estimated both before he took ammonium nitrate and while he was

taking it. Even after the ingestion of 10 Gm. of ammonium nitrate, a measurable amount could not be demonstrated in the feces; this indicates that absorption from the bowel was complete in this man.

CLINICAL USE IN CASES OF EDEMA

Method of Study.—In six cases of renal disease with edema, of which brief reports are appended, metabolic studies were done similar to those carried out on the four normal men. Some phase of metabolism of nitrates was studied, also, in twelve additional cases. The edema in these twelve patients was associated with renal or myocardial disease, cirrhosis of the liver, polyserositis or abdominal carcinomatosis. In the eighteen cases ammonium nitrate often was administered in enteric coated pills, each containing 0.5 Gm.[47] As the colorimetric method of Whelan for determining nitrates does not exclude the nitrites, care was taken that nitrites were not given for therapeutic purposes during these studies. An instance of a possible error of this sort was suggested in one case, for the patient had been given sodium nitrite for marked hypertension on the previous day. Estimations of certain constituents of the blood, urine and saliva were carried out as in the cases of the normal men. In a few cases, including case 5, the plasma chlorides were determined by the method of Wilson and Ball. This method, also, was applied to studies of the urine which contained protein. In addition, the concentration in the blood of creatinine nitrogen, protein, cholesterol and the content of water, as well as the concentration in the serum of total fixed base, sodium, potassium, calcium, magnesium, phosphorus and sulphate, were determined in some cases. The concentration of protein nitrogen in the urine was estimated. Simultaneous determinations were made of the concentration of nitrate nitrogen in the blood serum, edema fluid, fluid from the thoracic cavity and ascitic fluid both in cases of those patients who received and those who did not receive medication by nitrate.

In order to ascertain the actual amount of nitrate in the feces and to determine whether or not the presence of edema prevented digestion of the enteric coated pill or hindered absorption of ammonium nitrate from the bowel, estimations were made of nitrate in the feces, both before and after the ingestion of pills in four cases. In all, with the exception of one case, mere traces of nitrate were found. Possible failure to digest the coating of the pill or failure of absorption of nitrate in a single case would indicate that only rarely do untoward factors prevent ingested ammonium nitrate from entering the circulation. These results also show that excretion of nitrate by the bowel is minimal.

Action of Ammonium Nitrate.—The action of this substance on the blood was studied intensively in the six cases of renal disease with edema. In three instances the concentration of nitrate nitrogen in the plasma was determined. In two of the cases, of which reports are given at the end of this paper, (cases 3 and 5) and in which chronic nephrosis was present, the concentration of nitrate nitrogen in the plasma was as high as from 6 to 7 mg. in each 100 cc. This is distinctly higher than the concentration observed in the normal person, and yet urinary excre-

47. Enteric coated pills were used because nausea and vomiting less frequently follow their use. Ammonium nitrate in solution was troublesome in this respect.

tion was similar in both of these cases and in the normal person. The fall in the concentration of nitrate nitrogen was less rapid in case 5 than in the normal person. The observations in case 4, in which extensive edema was associated with chronic glomerulonephritis, are significant. There was obvious retention of nitrate, with a rapid rise of the concentration of nitrate in the plasma, to 19 mg. in each 100 cc. Instead of the usual rapid fall in the concentration of nitrate on discontinuing administration of ammonium nitrate, the decrease was slow and did not approach the normal value until the twentieth day. During this period, the concentration of nitrate in the edema fluid closely paralleled that of the plasma, and the daily urinary output was decreased and the total period of excretion of nitrate was prolonged. If we assume that only a very small amount of nitrate was absorbed before vomiting took place on the second day, approximately 86 per cent of the ingested salt was finally excreted during the period of twenty-two days.

The concentration of hemoglobin, as a rule, was little changed by administration of ammonium nitrate. In two experiments it was definitely increased. The concentration of urea nitrogen tended to remain stationary or fell. In case 4, there was a rise which undoubtedly was due to renal retention. The concentration of nonprotein nitrogen also tended to fall, except in two cases (cases 1 and 4). In case 1, the increase was not associated with a rise in urea, but with a diminished excretion of urinary protein, whereas in case 4 it was probably due to renal retention of urea. In two cases (cases 1 and 2), there was no significant change in the concentration of creatinine. The concentration of plasma chloride usually was increased, but varied little in the course of an experiment. In case 6, on one occasion, there was a distinct decrease. However, in this same case, the concentration of chloride in the edema fluid was very constant. As in the normal man, there was no significant change in the carbon dioxide combining power of the plasma. The amount of the total fixed base was determined on several occasions in case 5. There was a decrease from a high concentration in the control period in one experiment, and practically no change in another.

In order to test further the possible acid-base changes in blood serum or plasma, detailed quantitative analysis of certain constituents was made before and during the administration of nitrate. The patient (case 5) was selected for this study on his second admission, because of his previous good response to ammonium nitrate. The amounts of nitrate ingested and excreted in the urine were comparable to those ingested and excreted on the previous admission. The results of analysis of serum on both occasions were approximately identical, with the excep-

tion of a distinct increase in nitrate, a slight increase in protein, and a corresponding slight decrease in water content during the period of administration (table 12). In this case at least, with the increased nitrate content of the blood there was no change in many of the ions involved in the acid-base equilibrium. There was a slight reduction in water and an increase in protein that may have been due to a dehydrating effect of nitrate alone. Most of these patients with renal disease and edema retained nitrogen slightly during this period of ingestion of nitrate, and this may equally explain the increase in the concentration of serum protein. The effects on urinary excretion in these cases in which disease was present were similar to those seen in the normal men. There was a definite increase in volume and in the content of chlorides,

TABLE 12.—*Concentration of Serum Electrolytes Before and After the Administration of Ammonium Nitrate (Case 5)* *

	Dec. 2, 1929		Dec. 7, 1929	
	Mg. for Each 100 Cc.	Millimols	Mg. for Each 100 Cc.	Millimols
Chloride	367	104	358	101
Phosphorus	4.2	4.1	3.9	3.9
Sodium	314	136	317	137.5
Potassium	†	.....	20.3	6.6
Calcium	9.04	4.5	8.36	4.2
Magnesium	1.9	1.6	1.98	1.65
Sulphate	2.5	.....	.....	.....
Carbon dioxide	64.7‡	30.5	64.2‡	28.9
Protein	4.3	.....	4.8	.....
Nitrate nitrogen	0.11	.....	2.7	1.9
Water	94.6	.....	93.2	.....
Total fixed base (actual estimation)	.....	.....	.....	148

* 40 Gm. ammonium nitrate was given from Dec. 3, 1929, to Dec. 7, 1929.
† Determination not satisfactory.
‡ Per cent by volume.

nitrates and total fixed base. The increased hydrogen ion concentration and the increase in excretion of ammonia nitrogen were less evident. In a single case (case 3) the urinary sediment was examined daily and appreciable changes were not noted during the administration of ammonium nitrate. In case 2 the increased volume and the increased output of chloride continued for several days after the nitrate had been discontinued. On the other hand, in two cases during this second control period, there was a decrease in volume and concentration of chlorides comparable to that observed in the normal men. The slight increase in phosphate, sulphate and titratable acidity was even less than in the normal men.

The excretion of nitrate nitrogen in two cases of chronic lipoid nephrosis (cases 3 and 5) was similar to that in normal persons, although there was a tendency for the excretion to lag during the second control period. In case 4, one of chronic glomerulonephritis, there was marked

delay, with a resulting prolonged diminished daily output. In spite of this retention of nitrate, there was an initial increase in volume of urine, and in output of chlorides and of total fixed base. It was anticipated that retention of nitrate might occur in this case because there were other evidences of diffuse renal injury, for example, excretion of phenolsulphonphthalein of only 10 to 15 per cent in two hours and a somewhat fixed excretion of several urinary constituents. However, retention of nitrate to such a degree naturally was not expected.

One of the most specific effects of nitrates has been the excretion of chloride, fixed base and ammonia, when ammonium nitrate is administered. The increased excretion of both nitrate and chloride indicates that the tissues must neutralize two strong acids. Hence, with the administration of sodium nitrate there is a definite increase in fixed base, but the excretion of ammonia is not increased (normal man 3, tables 8 and 9). With ammonium nitrate, however, there is always a marked increase in both the excretion of fixed base and ammonia (normal man 3, tables 6 and 7, and case 5, tables 13 and 14). Averaging results over the entire period of ingestion of ammonium nitrate, the greater part of the acid is neutralized by ammonia. However, the available fixed base somewhat determines the degree to which the excess acid is neutralized by ammonia, as the figures for neutralization for each day will show. Calculations according to Fiske's [48] plan and figures, obtained from the three experiments, two of which were on subject 3, one on case 5 (tables 6, 7, 8, 9, 13 and 14), show that with the use of ammonium nitrate, from none to 60 per cent of the nitrate is bound by base and from 30 to 80 per cent by ammonia, whereas, with the use of sodium nitrate, practically all the nitrate is bound by fixed base, presumably from the sodium of the administered salt. Folling has shown that after the ingestion of ammonium chloride, a high percentage of the ingested chlorine is neutralized by ammonia.

The total nonprotein nitrogen, and the urea and ammonia fractions, were not uniformly increased by ingestion of ammonium nitrate. The excretion of ammonia nitrogen was prolonged in cases 1, 2 and 5, as in the normal men, but in case 4 it was scarcely altered from that of the control period in the same case. The concentration of creatinine nitrogen as a rule was constant, but in some cases the daily variation was greater than that found in normal persons. The excretion of protein nitrogen was variable; in some cases it increased; in others, it diminished. In two cases in which the concentration of urinary protein was diminished,

48. Fiske, C. H., and Sokhey, S. S.: Ammonia and Fixed Base Excretion After Administration of Acid by Various Paths, J. Biol. Chem. **63**:309 (March) 1925.

TABLE 13.—*Nitrogen Metabolism (Case 5)*

Date, 1929	Body Weight, Kg.	Nitrogen Intake: Total, Gm.	Food, Gm.	Ammonia, Gm.	Blood*: Non-protein Nitrogen, Mg. for Each 100 Cc.	Urea Nitrogen, Mg. for Each 100 Cc.	Total Fixed Base, Cc. N/10	Nitrate Nitrogen, Mg. for Each 100 Cc.	Urine: Volume, Cc.	Total Nitrogen, Gm., (Kjeldahl)	Protein Nitrogen, Gm.	Total Non-protein Nitrogen, Gm.	Urea Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Creatinine Nitrogen, Gm.	Feces, Total Nitrogen, Gm.	Urine and Feces, Total Nitrogen, Gm.	Comment
7/22	....	....	...	....	..	18	...	0.04	.....	....	....	.....	....	....	....	....	.....	
7/23-24	72.7	....	9.6	....	..	..	...	....	750	12.8	1.85	10.95	9.65	0.49	0.75	1.73	14.53	
7/24-25	72.7	....	9.6	....	..	..	...	....	500	9.1	1.75	7.35	6.85	0.24	0.53	1.21	10.31	
7/25-26	72.7	....	9.5	....	..	..	175	....	580	11.95	1.90	10.05	7.90	0.34	0.56	1.27	13.22	
7/26-27	72.3	....	9.5	....	50	20	...	....	550	11.0	2.15	8.85	7.70	0.37	0.53	0.67	11.67	Nitrogen balance (4 days), daily average, —2.9 Gm.
7/27-28	71.4	13.1	9.6	1.75	..	..	...	2.44	900	12.3	1.50	10.80	9.00	0.42	0.58	1.06	13.36	10 Gm. ammonium nitrate†
7/28-29	71.1	13.1	9.6	1.75	..	..	...	2.76	1,025	12.8	1.12	11.68	9.65	0.25	0.56	0.89	13.69	10 Gm. ammonium nitrate
7/29-30	70.0	11.3	9.6	0.875	..	..	...	4.7	950	11.3	0.85	10.45	8.45	0.98	0.49	1.72	13.02	5 Gm. ammonium nitrate, 5 Gm. vomited‡
7/30-31	70.0	13.0	9.5	1.75	..	..	...	5.2	875	11.2	0.90	10.30	8.92	0.78	0.46	1.30	12.50	10 Gm. ammonium nitrate
7/31-8/1	69.1	13.0	9.5	1.75	47	18	160	7.0	925	12.4	1.10	11.30	9.35	0.83	0.52	0.92	13.32	10 Gm. ammonium nitrate, total 45 Gm., 74 per cent nitrate ingested excreted in urine, nitrogen balance (5 days) daily average, —2.0 Gm.
8/1-2	69.5	....	9.5	....	..	..	...	3.3	675	9.65	0.75	8.90	6.65	0.88	0.50	2.48	12.13	
8/2-3	70.4	. ..	9.6	....	..	..	...	1.6	600	9.20	0.60	8.60	6.75	0.90	0.54	1.19	10.39	
8/3-4	70.5	....	9.6	....	..	..	...	0.9	450	8.35	1.20	7.15	5.23	0.86	0.43	1.68	10.03	
8/4-5	70.0	....	9.6	....	..	..	...	0.5	650	11.0	1.10	9.90	8.45	1.15	0.53	1.06	12.06	Nitrogen balance (4 days) daily average, —1.6 Gm., 89 per cent nitrate ingested excreted in urine

* Specimen of the blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution.

‡ Patient vomited 20 cc. of 25 per cent solution (5 Gm.) immediately after ingested, diet 2, additional daily water 600 cc.

TABLE 14.—*Mineral Metabolism (Case 5)*

Date, 1929	Nitrate Nitrogen Intake, Gm.	Blood*				Urine													Comment
		Plasma						Chloride		Phosphorus		Sulphate as Sulphur Trioxide		Nitrate Nitrogen					
		Hemoglobin, Gm. for Each 100 Cc.	Chloride, Gm. for Each 100 Cc.	Nitrate Nitrogen, Mg. for Each 100 Cc.	Carbon Dioxide Combining Power, per Cent by Volume	Volume, Cc.	p_H	Gm.	Cc. N/10	Gm.	Cc. N/10	Gm.	Cc. N/10	Gm.	Cc. N/10	Nitrate Nitrogen Balance, Gm.	Titratable Acidity, Cc. N/10	Total Fixed Base, Cc. N/10	Ammonia Nitrogen Gm.	Ammonia Nitrogen Cc. N/10	
7/22	....	....	...	0.04	70	.....	...	....	...	....	...	....	...	.....	...	.....	...	.....	....	...	
7/23-24	....	16.6	...	....	..	750	5.8	0.74	208	0.83	266	1.89	472	0.007	...	.....	428	790	0.49	350	
7/24-25	....	....	...	....	..	500	6.0	0.47	131	0.54	172	1.16	290	0.003	...	.....	260	500	0.24	168	
7/25-26	....	....	...	....	..	580	5.6	0.51	142	0.57	183	1.32	330	0.005	...	.....	313	575	0.34	240	
7/26-27	....	....	345	....	70	550	5.6	0.37	105	0.67	215	1.26	315	0.004	...	.....	335	530	0.37	262	
7/27-28	1.75	....	...	2.44	..	900	5.4	2.45	690	0.65	208	1.35	337	0.675	535	+1.08	315	840	0.42	302	10 Gm. ammonium nitrate given†
7/28-29	1.75	....	...	2.76	..	1,025	5.4	2.89	815	0.78	250	1.35	337	1.26	900	+0.49	380	1,580	0.25	176	10 Gm. ammonium nitrate given
7/29-30	0.875	....	...	4.7	..	950	5.6	2.64	745	0.71	230	1.45	362	1.45	1,035	−0.57	304	1,650	0.98	700	5 Gm. ammonium nitrate given, 5 Gm. ammonium nitrate vomited
7/30-31	1.75	....	...	5.2	..	875	5.6	1.96	552	0.64	206	1.43	357	1.19	850	+0.56	368	1,520	0.78	555	10 Gm. ammonium nitrate given
7/31-8/1	1.75	....	359	7.0	51	925	5.6	2.00	563	0.79	253	1.65	413	1.17	780	+0.58	370	1,340	0.83	590	10 Gm. ammonium nitrate given, total 45 Gm. 74 per cent nitrate ingested excreted in urine
8/1-2	....	....	...	3.3	..	675	5.6	0.62	175	0.68	220	1.40	350	0.60	430	−0.60	316	500	0.88	625	
8/2-3	....	....	...	1.6	..	600	5.8	0.33	93	0.60	194	1.42	355	0.32	230	−0.32	220	282	0.90	640	
8/3-4	....	....	...	0.9	..	450	6.0	0.19	54	0.43	139	0.87	220	0.149	108	−0.15	151	171	0.86	615	
8/4-5	....	....	...	0.5	..	650	6.0	0.12	33	0.57	184	1.62	405	0.059	42	−0.06	168	215	1.15	825	89 per cent nitrate ingested excreted in urine

* Specimen of the blood taken before breakfast at end of twenty-four hour period; diet 2, additional daily water 600 cc.
† Given in 25 per cent solution.

the concentration of nonprotein nitrogen of the blood was increased or remained elevated. The ratio of inorganic sulphate to total nitrogen was approximately constant.

Studies of nitrogen balance were carried out in five cases during an initial control period. In case 1 the condition was one of nitrogen equilibrium; in cases 3 and 4 the condition was one of positive balance, whereas in cases 2 and 5 (table 5) it was one of negative balance. These variable phenomena, in cases of edema, are comparable with those observed in the normal subjects and emphasize the importance of an initial control period before the attempt is made to determine the effect of the test substance. During the ingestion of ammonium nitrate in cases 2 and 5, the negative balance decreased, or, in other words, a relative positive balance had developed; in case 1 there was an actual positive balance, and in case 4 the previous positive balance continued to be present. These results in cases of edema indicate that during the ingestion of ammonium nitrate there is usually absolute or relative retention of nitrogen. In case 4 this probably was due to continued retention of urea; in case 1, to retention of both urea and urinary protein, and in cases 2 and 5 to storage of nitrogen in the extrarenal tissues. There is now good evidence that extrarenal storage of nitrogen occurs in many cases of renal edema. This is particularly true after diuresis has occurred and convalescence is established.

After ingestion of ammonium nitrate, the concentration of nitrate in the saliva was definitely increased above the normal, as was noted by Ville and Mestrezat [49] after administration of sodium nitrate, but the concentration was much less in degree in the saliva than in the urine.

The comparative concentrations of nitrate nitrogen in the blood plasma or serum and in edema fluid, fluid from the thoracic cavity and ascitic fluid were determined in several cases of edema, both before and during the administration of ammonium nitrate. Similar concentrations were the rule, but occasionally there were measurable differences. These observations emphasize that nitrates penetrate readily into the tissues of the whole body, a property that might be expected of such readily soluble and diffusible salts.

Toxic Effects.—Toxic symptoms due to abnormally large doses of nitrates, particularly potassium nitrate, have been reported repeatedly since Alexander's description [50] in 1773. The use, twenty years ago, of bismuth subnitrate in large amounts, for diagnostic purposes, led to

49. Ville, J., and Mestrezat, W.: Origine des nitrites contenus dans la salive; leur formation par réduction microbienne des nitrates élimenés par ce liquide, Compt. rend. Soc. de biol. **63**:231 (July) 1907.

50. Alexander, William, quoted by Jörg (footnote 2).

several cases of nitrate poisoning accompanied by methemoglobinemia.[5] Since the introduction of ammonium nitrate as an effective diuretic four years ago, the drug has been taken by several normal persons and by a large number of patients in doses of 6 to 10 Gm. daily, with remarkably few toxic manifestations. Christian,[51] and Barker and O'Hare,[52] in 1928, reported cyanosis and methemoglobinemia without other toxic symptoms, in a patient with nephritis and edema who was receiving 15 Gm. of ammonium nitrate daily. Since May, 1928, we have observed the occurrence of cyanosis and methemoglobinemia in three patients who were receiving diuretic treatment including ammonium nitrate. The results in two cases were reported by Eusterman and Keith [53] in 1929. One of these patients received, at another time, 24 Gm. of ammonium nitrate over a period of three days, and again methemoglobinemia was produced. Striking untoward symptoms did not develop, and cessation of administration of the drug led to rapid disappearance of the cyanosis and methemoglobinemia. The third patient, one with chronic nephrosis, received 10 Gm. daily and the same untoward conditions developed after ingestion of approximately 122 Gm. In all three cases definite dysfunction of the intestine was present in the form of chronic obstruction or marked constipation. This fact leads one to consider the possibility of some abnormal function, such as bacterial action in the intestine, which could cause reduction of the nitrate to nitrite, and the formation of methemoglobin. On the other hand, the lack of cyanosis in case 4, in which there was marked retention of nitrate for several days, indicates that nitrates in considerable amounts may be widely distributed throughout the body without giving rise to gross methemoglobinemia. Similarly, nitrites may be present without methemoglobinemia developing, for Binz [54] showed that sodium nitrite could be given experimentally in doses large enough to produce a narcotic-like action, without change in the color of the blood.

Minor toxic symptoms, such as nausea and vomiting, occasionally appeared shortly after small amounts of the drug had been given in solution. This observation led to the use of enteric coated pills, which have proved to be more satisfactory. Diarrhea has scarcely been men-

51. Christian, H. A.: Discussion, Tr. A. Am. Phys. **43**:290, 1928.

52. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec.) 1928.

53. Eusterman, G. B., and Keith, N. M.: Transient Methemoglobinemia Following Administration of Ammonium Nitrate, M. Clin. North America **12**:1489 (May) 1929.

54. Binz, C.: Ueber einige neue Wirkungen des Natriumnitrits, Arch. f. exper. Path. u. Pharmakol. **13**:133 (Oct.) 1881.

tioned by subjects used as normal controls or by patients. Caution must be used in giving any ammonium salt to a patient with an abnormally high concentration of blood urea. This danger signal we previously emphasized when advocating the use of ammonium chloride.[55] With the usual rapid excretion of nitrate in the urine, toxic symptoms rarely occur.

The toxic features that developed in case 4, during marked retention of nitrate, are of great interest. The patient's symptoms were headache, asthenia, nausea, vomiting and drowsiness, and at times mild delirium was present. Similar toxic gastro-intestinal symptoms were graphically described by Alexander, in 1773, in the case of a woman who had taken a massive dose of potassium nitrate. The blood pressure, which previously had averaged 155 systolic, and 100 diastolic, was increased to 200 systolic and 125 diastolic, and remained thus elevated for ten days during the period of retention of nitrate. Cyanosis, such as one observes in methemoglobinemia, was not present, nor were severe retention of urea and acidosis present. The possibility of increased concentration of ammonia in the blood and tissues could not be excluded, although a concentration high enough to produce toxic symptoms seems unlikely. These observations support the view that the toxemia was caused by the nitrate ion. Prompt estimation of nitrate in the blood should give early warning and should prevent marked retention of nitrate such as that which occurred in a single case of this series.

Long-continued daily ingestion of doses of from 8 to 10 Gm. was carried out in three cases without any toxic manifestations. The total amount ingested in these three cases was 250 Gm. in twenty-five days, 478 Gm. in fifty-six days, and 295 Gm. in thirty days. As much as 560 Gm. was administered to the latter patient during the entire period of hospital treatment, without toxic symptoms.

COMMENT

These studies show that nitrates are efficient diuretics. The diuretic response is accompanied by certain specific metabolic changes which involve the inorganic salts, the acid-base equilibrium, water balance and the nitrogen balance. The best results were obtained by the use of ammonium nitrate, apparently because, on absorption, the ammonium radical is readily converted into urea, leaving the nitrate portion of the

55. Keith, N. M.; Barrier, C. W., and Whelan, Mary: The Diuretic Action of Ammonium Chlorid and Novasurol in Cases of Nephritis with Edema, J. A. M. A. **85**:799 (Sept. 12) 1925.

molecule free to act. The concentration of nitrate in the blood rises considerably, and nitrate is readily excreted by the kidney. In man, as much as 90 per cent of the nitrate ingested has been recovered in the urine, indicating that only small amounts are excreted through other channels or are taken care of by the organism in other ways. The smaller amount excreted by the dog in our experiments may be due to the fact that administration was by the intravenous route or because sufficient time was not allowed for excretion. These results suggest that nitrate might be usefully employed as a test of renal function. In contrast to the results obtained by Mitchell, Shonle and Grindley,[56] there is little evidence in our experiments that considerable amounts of nitrate are destroyed in the human body. In our work, as in that previously done by others, systemic nitrite-like actions did not occur, with the exception of the rare development of methemoglobinemia. Thus, the reduction of nitrates to nitrites rarely occurs in animals, although Kastle and Elvove [57] have shown that certain extracts of plants in vitro have reducing action. The increased concentration of nitrate in the saliva is evidence of its diffusibility and possible wide distribution throughout the body. Nitrates cause disturbance of the metabolism of inorganic salts, especially of the chlorides. It is of interest that an increased concentration of one anion (nitrate) should cause increased excretion of another anion (chloride). The retention of salts is similar to that following the diuresis produced by many other substances.[58] The disturbance in the acid-base equilibrium toward the acid side is not sufficiently great in man to produce significant reduction in the carbon dioxide combining power of the plasma, but it does cause an increase in the hydrogen ion concentration of the urine, and a markedly increased excretion of fixed base and ammonia. In a single experiment retention of nitrogen occurred.

The action of ammonium nitrate in cases of edema was similar to but not as uniform as its action in the normal subject. The concentration of nitrate in the blood rose to a higher level, and the excretion in the urine was not so rapid. The content of nitrate in edema fluid usually closely paralleled that of the blood plasma. The diuretic and metabolic

56. Mitchell, H. H.; Shonle, H. A., and Grindley, H. S.: The Origin of the Nitrates in the Urine, J. Biol. Chem. **24**:461 (April) 1916.

57. Kastle, J. H., and Elvove, Elias: On the Reduction of Nitrates by Certain Plant Extracts and Metals, and the Accelerating Effect of Certain Substances on the Progress of Reduction, Am. Chem. J. **31**:606, 1904.

58. Keith, N. M., and Whelan, Mary: Changes in Body Temperature and Metabolism Accompanying Experimental Marked Diuresis, Am. J. Physiol. **77**: 688 (Aug.) 1926.

effects often were slower in beginning, but once started were, as a rule, more prolonged. In some instances, active diuresis persisted for several days after ingestion of ammonium nitrate was discontinued. These results indicate that the rapidity and extent of the action of nitrate depend in part on the amount and composition of the edema fluid, and also on the degree of restoration of the normal current of fluid from tissues to blood and from blood to urine. When severe renal injury is present, marked retention of nitrate may occur and may cause specific toxic symptoms.

The disturbance of the acid-base equilibrium is of interest. The bicarbonate of the blood plasma is not reduced. The initially increased urinary excretion of acid radicals is accompanied by a relatively larger amount of fixed base than of ammonia, but with continued action, the amount of fixed base diminishes as that of ammonia proportionately increases.

Keith and Whelan,[6] and Folling, after ingestion of ammonium chloride, and Gamble and his co-workers, after ingestion of calcium chloride, have demonstrated urinary data similar to those observed after ingestion of ammonium nitrate. However, Folling concluded that the diuresis occurred only when the increased acid was neutralized by a relatively large proportion of fixed base. Both with ammonium chloride and ammonium nitrate, we are unable to find such an exact relationship. The different specific biochemical effects of two inorganic anions, such as chloride and nitrate, are of significance. Both produce changes in the acid-base equilibrium. The nitrate causes much less change in the bicarbonate of the blood than the chloride, and yet the diuresis produced is greater.

Both relative and actual retention of nitrogen may occur. Two causative factors at least must be considered: (1) diminished ability of the kidney to excrete urea or protein, and (2) actual retention of nitrogen in the tissues due to extrarenal factors.

The actual site of the diuretic action of nitrates is not definitely known. If their action is entirely renal, the loss of water and salts eventually affects the general tissue metabolism. The present studies indicate that their action is a combined one and that they affect both the kidneys and the tissues generally. Primarily, the nitrate ion would appear to have a specific action on the tissues, which causes liberation of water and chlorides. This effect, in our opinion, is not entirely due to increase in hydrogen ion concentration, as has been suggested for ammonium chloride, nor does it seem to be a simple substitution of nitrate for chloride, similar to that of iodide or bromide for chloride.

Loewi [59] suggested that such a substitution takes place, but Sollman [60] and Cushny,[61] with both of whom we agree, do not believe the experimental data can be fully explained on this basis. If a specific effect on the cells and tissues does occur, conceivably metabolism of protein could be affected, and thus the altered excretion of nitrogen, sulphate and phosphate sometimes observed in our experiments could be explained. It might also explain the initiation of the accelerated current of fluid from tissue to blood and from blood to urine. Such a possible process is in harmony with the demonstration by Curtis [62] that intraperitoneal injections of certain solutions may profoundly alter the diuretic response to administration of caffeine to rabbits.

Schlosser,[63] in 1913, showed experimentally that the combined use of caffeine and sodium sulphate produced greater diuresis than either of these substances alone. Similar results were obtained by us with ammonium chloride and with an organic compound of mercury, and in this study, also, by ammonium nitrate and organic compounds of mercury. Both of these ammonium salts, organic compounds of mercury, and caffeine cause a saline type of diuresis. Further combinations of diuretics should prove to be of theoretic interest, and possibly should lead to greater beneficial results in the treatment of dropsy.

Toxic phenomena rarely have occurred. The use of enteric coated pills containing ammonium nitrate has lessened the occurrence of nausea and vomiting. When the rare instances of methemoglobinemia do occur, there are no annoying subjective or toxic symptoms, and simple withdrawal of the drug results in rapid disappearance of the cyanosis. The occurrence of actual toxic effects from too high a concentration of nitrate in the body fluids can be avoided. Effective measures against toxic effects are preliminary tests of renal function and, on the first suspicion of toxemia, estimation of the nitrate content of the blood.

REPORT OF CASES

Following are brief reports of the six cases in which complete metabolic studies were made.

59. Loewi, Otto: Untersuchungen zur Physiologie und Pharmakologie der Nierenfunction, Arch. f. exper. Path. u. Pharmakol. **48**:410 (Dec.) 1902.

60. Sollman, Torald: The Effect of Diuretics, Nephritic Poisons and Other Agencies on the Chlorides of the Urine, Am. J. Physiol. **9**:425 (Aug.) 1903.

61. Cushny, Arthur R.: The Secretion of the Urine, ed. 2, New York, Longmans, Green & Company, 1926, pp. 189-190.

62. Curtis, G. M.: Die Wirkungsweise der spezifischen Diuretica nebst Beiträgen zur Lehre von der Harnabsonderung, Biochem. Ztschr. **163**:109, 1925; Die Wirkungsweise der spezifischen Diuretica, Klin. Wchnschr. **4**:824 (April) 1925; The Action of the Specific Diuretics, J. A. M. A. **93**:2016 (Dec. 28) 1929.

63. Schlosser, K.: Ueber die Wirkung kombinierter Diuretica, Ztschr. f. d ges. exper. Med. **1**:559, 1913.

Case 1.—A woman, aged 40, came to the clinic on Oct. 16, 1927, with the complaint of dropsy. In 1919, she had had edema of the lower part of the legs for three months. The present illness had begun two months previously, with dependent edema, which gradually spread over the whole body. General examination showed moderate general edema, most marked in the dependent parts. Definite objective abnormalities in the cardiovascular system were not observed. The blood pressure was 140 systolic and 90 diastolic. The ocular fundi were normal. Urine showed marked albuminuria with a few erythrocytes, leukocytes and double refractive lipoid substances. The blood urea nitrogen was 10 mg., the blood creatinine 1.2 mg., serum proteins 3.6 Gm., with 50 per cent albumin, and blood cholesterol 500 mg. in each 100 cc. The hemoglobin (Dare) was 70 per cent; erythrocytes numbered 4,130,000. The excretion of phenolsulphonphthalein was 45 per cent in two hours. During the period of treatment in the hospital, the edema disappeared, with a loss of 9 Kg. in body weight.

The patient returned for examination in June, 1928. The blood pressure was 150 systolic and 105 diastolic; erythrocytes numbered 3,670,000. The ocular fundi showed changes of hypertension in the retinal arteries and one resolving exudate. The subsequent course was that of slowly progressive failure, and the patient died on April 6, 1929. The diagnosis was chronic glomerulonephritis.

Case 2.—A colored man, aged 30, registered at the clinic on Dec. 30, 1927. Two and a half years previously, edema of the face and legs, hematuria, albuminuria and oliguria had developed; the illness lasted for three weeks, and he thought that he had recovered from it. Two and a half months before admission, edema had begun, and in a short time general anasarca developed. Dyspnea, oliguria and hematuria were also present. On general examination there was orthopnea and marked general anasarca, left hydrothorax and ascites. The blood pressure was 170 systolic and 120 diastolic. The ocular fundi were essentially normal. The urine contained large amounts of albumin, a few casts, leukocytes and double refractile bodies, but no erythrocytes. The hemoglobin (Dare) was 73 per cent; erythrocytes numbered 3,850,000. The Wassermann reaction of the blood was strongly positive. The blood urea nitrogen was 15 mg., creatinine 2 mg., serum proteins 3.3 Gm., of which 38 per cent was albumin, and the blood cholesterol, 338 mg. The excretion of phenolsulphonphthalein was 40 per cent in two hours. During treatment in the hospital with ammonium nitrate and mersalyl, striking and lasting diuresis occurred, with the disappearance of the edema and a loss of 37.6 Kg. in body weight. The diagnosis was chronic glomerulonephritis with anasarca.

Case 3.—A girl, aged 15, was admitted to the clinic on April 11, 1929. Two and a half months before admission, the patient had had an acute sore throat for five days. Two weeks later she noticed the gradual onset of generalized edema which became marked and resistant to treatment. She had gained 16 Kg. since the onset of the illness. General examination showed general anasarca. The tonsils were enlarged and infected. The ocular fundi were normal. The blood pressure was 120 systolic and 80 diastolic. Urinalysis showed marked albuminuria and some casts, but no blood cells. Hemoglobin (Dare) was 70 per cent; erythrocytes numbered 4,400,000. The blood urea nitrogen was 6 mg., creatinine 1 mg., serum proteins 3.3 Gm., of which 46 per cent was albumin, and blood cholesterol 501 mg. Following treatment in the hospital for one month, the edema disappeared and loss in weight amounted to 11.8 Kg. Two days after tonsillectomy, fever developed and later there was evidence of general peritonitis and septicemia. The patient died on the fifth day after tonsillectomy. At necropsy,

general peritonitis was found; the kidneys together weighed 423 Gm. and resembled the large pale kidneys of chronic nephrosis. Microscopic study showed the characteristic changes of chronic nephrosis without definite glomerulonephritis.

Case 4.—An unmarried woman, aged 24, registered at the clinic on May 21, 1929. Eight months previously she had first noticed edema of the feet, and general anasarca subsequently developed rapidly. On general examination, the mucous membranes were pale, and extreme general anasarca was present. The ocular fundi showed some neuroretinal edema. The blood pressure was 170 systolic and 120 diastolic. Urinalysis showed a high content of albumin and many casts, but no erythrocytes. The hemoglobin (Dare) was 50 per cent; erythrocytes numbered 2,800,000. The blood urea nitrogen was 11 mg., serum proteins 3.2 Gm., of which 30 per cent was albumin, and blood cholesterol 398 mg. The excretion of phenolsulphonphthalein was 15 per cent in two hours. Following the use of ammonium nitrate, diuresis resulted, but within a few days toxic manifestations developed and the drug was discontinued. At the time of dismissal, eighty-five days after admission, the patient was almost free from edema, having lost 37 Kg. in weight. The diagnosis was chronic glomerulonephritis with anasarca. The prognosis was guarded.

A second examination was made on Nov. 4, 1929. There had been definite improvement. The blood pressure was 130 systolic and 90 diastolic. The blood urea nitrogen was 16 mg. The excretion of phenolsulphonphthalein was 25 per cent in two hours. A letter in March, 1930, stated that the patient is still improving.

Case 5.—A man, aged 24, registered at the clinic on July 16, 1929. He had first noticed edema in March, 1929, which gradually became generalized, and which persisted until admission. General examination showed marked general anasarca. The ocular fundi were normal. The blood pressure was 130 systolic and 90 diastolic. Urinalysis showed a high content of albumin, some casts and a few leukocytes, but no erythrocytes. The hemoglobin (Dare) was 75 per cent; erythrocytes numbered 4,430,000. The blood urea nitrogen was 22 mg., the creatinine 1.5 mg., the serum proteins 3.6 Gm., of which 39 per cent was albumin, and the blood cholesterol 337 mg. The excretion of phenolsulphonphthalein was 65 per cent in two hours. Following treatment, the edema disappeared, with a loss of 18 Kg. in weight. The diagnosis was chronic lipoid nephrosis.

A second examination was made on Dec. 2, 1929. There was slight recurrence of edema and a recent infection of the upper respiratory tract. The data were essentially the same as before. A third examination was made on Feb. 5, 1930. Edema or anemia was not present. The other data were the same as on the former visits.

Case 6.—A man, aged 47, was admitted to the clinic on Jan. 23, 1928. There had been gradual development of edema which had begun four months previously. On general examination there was moderate general anasarca and some ascites. The blood pressure was 120 systolic and 90 diastolic. The ocular fundi appeared normal. The urine contained a large amount of albumin, numerous casts, a few leukocytes and double refractive bodies, but no erythrocytes. The hemoglobin (Dare) was 70 to 75 per cent; erythrocytes numbered 4,000,000. The blood urea nitrogen was 12 mg., blood creatinine 1.8 mg., serum proteins 3.5 Gm., of which 44 per cent was albumin, and blood cholesterol 309 mg. The excretion of phenolsulphonphthalein was 65 per cent in two hours. During treatment, the edema disappeared and the patient lost 13.6 Kg. in weight. The diagnosis was chronic lipoid nephrosis.

SUMMARY

The diuretic action of nitrates has been confirmed by the extensive use of ammonium nitrate. The action involves certain specific metabolic changes which result from the liberation of salts and water from the tissues. Nitrate reaches a considerable concentration in the blood and edema fluid, and is readily excreted by normal kidneys and by those which have undergone certain pathologic changes. Rare toxic conditions can be prevented or effectively treated. Further diuretic action can be obtained by combining the administration of nitrate with that of other diuretics.

PERIPHERAL NEURITIS COMPLICATED BY MASSIVE COLLAPSE OF THE LUNG FOLLOWING TONSILLECTOMY*

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DETROIT

The following case is submitted because of a threefold point of interest, i. e.: (1) the development of a multiple peripheral nerve paralysis in the presence of an existing renal tuberculosis; (2) the occurrence of massive collapse of the lung following tonsillectomy, and (3) the clearing up of the paralyses following removal of the foci of infection.

REPORT OF CASE

History.—A white man, aged 39, an ironworker, entered the hospital on Aug. 31, 1928, complaining of weakness of the arms and paralysis of the legs of a gradually progressive nature. He dated the onset of his symptoms about two and a half months prior to his admission, and stated that it followed his recovery from an attack of left lobar pneumonia. The early symptoms consisted of a tingling sensation in the fingers and toes followed in three weeks by weakness, which first appeared in the knees. A gradually increasing loss of strength developed in the legs and started in the arms. Ten days prior to admission, he lost the use of his legs entirely. Meanwhile the loss of power in the arms continued, and at the time of admission he could move the fingers and arms, but had very little strength in them.

Two years previously a diagnosis of renal tuberculosis on the right side had been made, and at that time tubercle bacilli had been demonstrated in the urine. Operation for the removal of this kidney was advised but was refused, and no other treatment had been instituted in the interval. The only symptom he complained of relative to the kidneys at this time was a frequency of urination.

He had had measles in childhood, influenza in youth and lobar pneumonia in May, 1928, prior to the present illness. There was no history of injuries or operations.

The patient said that he was an ironworker and had been for six years. This work required fairly heavy physical exertion. He secured an abundance of outdoor exercise and fresh air. He was accustomed to eight or nine hours of sleep at night and usually rested well. Coffee and tobacco were used in moderation and alcohol rarely. His average weight was given as 135 pounds (61.2 Kg.); he had lost approximately 15 pounds (6.8 Kg.) during his recent illness.

There were no symptoms referable to the cardiovascular or gastro-intestinal system. Frequency of urination, urgency, nocturia and cloudy urine were present at irregular intervals for two years.

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* From the Department of General Medicine, Henry Ford Hospital.

His father and mother were living and in good health. There was no history of tuberculosis, diabetes, nervous diseases, mental disorders, cancer, hemophilia or goiter in the family.

Physical Examination.—The patient was moderately undernourished; he was not acutely ill nor in evident distress. The weight could not be secured on account of the paralysis of the legs. The temperature was 98.6 F.; the pulse rate 90, and respirations 16 to the minute.

The hair was sparse and dark and was of the average quality and texture. The skin was smooth, warm and rather moist. It was unusually shiny over the lower half of the arms and legs.

The pupils reacted well to light and in accommodation. The extra-ocular movements were normal. Ophthalmoscopic examination showed the media to be clear, the outlines of the disks sharp, normal cupping and the usual retinal observations.

There was bilateral, partial deafness. A slight amount of mucopurulent discharge came from the left ear. The Weber test was lateralized to the left. Bone conduction was better than air conduction on the two sides.

The sense of smell was unimpaired. Nothing unusual was observed in the nasal cavities.

The gums showed a rather widespread active pyorrhea. Several teeth appeared to be devitalized. The tonsils were small, scarred and embedded and showed moderate retention. Pus was easily expressed from the left side. The pharynx was moderately congested, and some mucopurulent material adhered to the posterior pharyngeal wall.

There was no general glandular enlargement. The anterior cervical glands draining the tonsils were enlarged. The axillary, inguinal and epitrochlear glands were not palpable.

The thyroid gland was small and deeply set. No nodules were felt.

The chest was narrow and of the asthenic type. Expansion was good. The bases of the lungs descended equally on the two sides. Litten's sign was positive bilaterally. There was some impairment of the percussion note over the left upper part of the chest posteriorly. Tactile and vocal fremitus were considered normal. The breath sounds were unimpaired, except for questionable muffling over the left upper posterior portion of the chest. No posttussic râles were elicited in the upper half of either lung.

The apex impulse of the heart was not visible but was palpable in the fifth intercostal space, 8 cm. from the left of the midsternal line. Dulness extended 9 cm. to the left and 2 cm. to the right. The heart tones were of good quality, and the rhythm was regular. No murmurs or accentuations were heard. The pulse rate was 80 to the minute and was of good volume and tension. The arterial walls were not thickened. The blood pressure was 158 systolic and 100 diastolic.

The abdomen was ovoid, soft and relaxed. The liver and spleen were not felt. There was slight tenderness over the transverse colon. No herniations or ascites were present. Posteriorly, there was deep tenderness to massive percussion over the right kidney.

The right testicle was retracted, and there was a small hard nodule in the region of the globus major. The left testicle was considered normal. The prostate was of normal size, shape and consistency.

There was a flaccid motor paralysis of the lower extremities. The arms could be moved but very weakly, especially at the wrist. Movement was slightly stronger at the elbows and the shoulders. There was a peculiar gloss to the skin of the

hands and feet. There was evidence of moderate muscle atrophy in both legs and arms. The deep reflexes were abolished in the legs. Those in the arms were still present, but responded weakly. The abdominal reflexes were not elicited. The cremasteric reflexes were present and active. Babinski's sign was negative bilaterally. Sensation to touch was impaired 2 per cent over the lower legs and the hands. Pain and temperature were unimpaired. Deep pressure to the calves caused considerable pain. The vibratory sense was lost over the feet and tibiae.

Laboratory Data.—On September 1, the specific gravity of the urine was 1.018; the urine was lemon-colored and cloudy. The albumin test gave a 3 plus reaction. The guaiac test gave positive results. The test for sugar was negative. The urine contained many coarsely granular casts and red and white blood cells. On September 1, the phenolsulphonphthalein test showed an excretion of 54 per cent in two hours; on September 5, an excretion of 57 per cent in two hours. Acid-fast bacilli were found in several twenty-four hour specimens of urine. Positive cultures of the tubercle bacilli were obtained from the urine coming from the right kidney during ureteral catheterization.

Examination of the blood showed: red cells, 5,200,000 per cubic millimeter; hemoglobin, 15.3 Gm. per hundred cubic centimeters; white cells, 10,800; differential count: polymorphonuclear neutrophils, 71 per cent; polymorphonuclear eosinophils, 1 per cent; small monocytes, 25 per cent; large monocytes, 3 per cent. The patient's blood belonged to type 4. The Wassermann reaction was negative according to the Kolmer and Kahn technic. The chemical analysis of the blood showed: nonprotein nitrogen, 40 mg., urea, 17 mg. and sugar, 91 mg. per hundred cubic centimeters.

Macroscopic examination of the feces showed no undigested food particles, blood or pus. Microscopic examination revealed no red or white cells, ova or parasites. The guaiac test gave negative results. Several specimens of stools and urine were negative for lead. The stools were persistently negative for acid-fast organisms.

The spinal fluid was clear. The globulin reaction was negative. The spinal fluid contained 3 cells, with a pressure of 16 mm. of mercury. The Wassermann reaction was negative. The spinal fluid contained 59 mg. of sugar per hundred cubic centimeters. The Lange test gave a reaction of 0000112210; the mastic test, 2332210000. The test for lead gave negative results.

Roentgen Reports.—The stomach was empty on the nine hour examination. There was some barium sulphate collected in the terminal ileum and some traces in the cecum and the ascending colon. An enema of barium sulphate showed the colon to be well filled throughout and normal in contour. There was considerable redundancy of the sigmoid portion.

The upper left central incisor tooth had an extensive area of caries in the crown. The upper right central incisor and cuspid were both carious. The lower left first molar was devitalized. There was a diffuse area of lessened density involving the apices of the upper left cuspid and first bicuspid.

There were several small shadows of increased density in the region of the right kidney. A pyelogram showed the upper calyx of the right kidney to be well filled and normal in outline. The middle calyx was large and irregular in outline. The left kidney was considered normal.

No pathologic changes were noted in the cervical spine.

Diagnoses.—The following diagnoses were made: renal tuberculosis of the right kidney; tuberculous epididymitis; peripheral neuritis; oral sepsis—pyorrhea, devitalized teeth and periapical rarefaction—chronic tonsillitis; chronic otitis media.

Progress.—The temperature remained normal or below for thirty days. The pulse rate ranged between 80 and 100. The respirations ranged from 16 to 20.

The patient was given general upbuilding therapy, i. e., rest in bed, high caloric diet, treatments with the ultraviolet light and physical therapy. The weakness of the arms progressed for the first two weeks. This continued until the hands could just be moved, then the condition became stationary. At this time all the devitalized and suspicious teeth were extracted. The patient was transferred to the nose and throat division one week later, where a tonsillectomy was performed under local anesthesia.

On the morning of the first day following the operation, he experienced an acute attack of dyspnea accompanied by palpitation and cyanosis. The pulse rate rose to 130 and a few hours later to 160. The temperature rose to 100 F. The dyspnea and cyanosis increased until the condition became alarming. The patient was in acute distress, panting for breath and very cyanotic. There was infrequent coughing, with expectoration of small mounts of tenacious mucoid sputum. No pain was experienced. The chest showed limitation of motion on the left side. There was hyperresonance to percussion over the right side, and many coarse moist râles were heard anteriorly below the level of the third rib. The lower left side of the chest exhibited distant breath sounds and impaired resonance. The apex impulse of the heart was forceful and heaving and was visible and palpable in the left anterior axillary line in the fourth interspace. The cardiac dulness extended 14 cm. to the left of the midsternal line and merged with the impaired resonance already noted in the lower left side of the chest. The right border of the heart was not percussable due to the hyperresonance of the right side of the chest. The pulse was very feeble and rapid. The blood pressure at this time was 80 systolic and 50 diastolic. The abdomen was soft and tympanitic and showed no unusual changes. Roentgen examination of the chest showed a marked elevation of the diaphragm, displacement of the heart to the left and a patchy infiltration of the lower lobe of the left lung. The observations were characteristic of massive collapse of the lung on the left side.

The patient was in a critical condition for three days, requiring almost continuous administration of oxygen. Then the general condition seemed to improve, the cyanosis lessened and the dyspnea was relieved. The pulse rate continued high, however, and the temperature rose to a higher level. Physical signs in the chest, verified by roentgen examination, denoted an increasing mobility of the left side of the diaphragm, a return of the heart to the right, and also bronchopneumonia on the right side. The latter progressed until it involved the major portion of the lower lobes of both lungs. The temperature reached a maximum of 103.2 F. on the tenth day and began to subside. The leukocytes increased to a maximum of 21,000, with 92 per cent polymorphonuclear elements. The nonprotein nitrogen rose to 68 mg. per hundred cubic centimeters. The sputum remained persistently negative for acid-fast organisms, streptococci being present in numbers. Several blood cultures were reported negative. The urine continued to show large quantities of albumin, casts and red and white cells.

On the tenth day following onset of the pneumonia, a sharp rise again occurred in the temperature curve, and the leukocytes rose to 31,400. It was thought that this might be indicative of the formation of an abscess of the lungs, empyema or a general dissemination of the tuberculosis from its focus in the urinary tract. Serial x-ray films of the lungs showed moderate resolution of the pneumonic process in the right lung, but little change on the left side. No pleural exudate was noted.

Meanwhile notable changes were occurring in the neurologic condition. The patient noted that he could use his arms and hands with increasing ease, and he regained the use of his legs to a slight extent, being able to lift his knees from the bed and wriggle his toes.

Neurologic examination at this time showed a definite muscular hypertonus but generalized extensor weakness, the flexor reflexes showing the greater return of function. The grips were definitely present, but could not be reliably recorded on the dynamometer. The patient was able to move the legs, flex the ankles and move the toes. There was no stiffness of the neck. The deep tendon reflexes were very much diminished generally. The biceps and triceps reflexes were obtained but the knee and ankle jerks could not be elicited even with the reinforcement that he was able to give. Pathologic signs in the toes or ankle clonus was not present. The cremasteric reflexes were very brisk. The lower abdominal reflexes could be elicited. There was a definite obtundity of all the sensory receptors, most marked in the lower extremities below the knees. Deep nerve tenderness was present to a moderate degree.

From this time on the course assumed a toxic character. The fever became septic, and the patient manifested progressive emaciation and toxicity. The breath became foul, and x-ray films of the chest revealed observations indicative of an abscess of the lungs. X-ray films of the chest taken after the intratracheal administration of iodized poppy seed oil, 40 per cent, did not localize the abscess satisfactorily. Medical treatment failed to modify the downward course, and thoracotomy was done in an effort to drain the abscess surgically. The patient did not survive the operation.

Autopsy.—Partial postmortem examination was done. The observations were as follows:

The body was that of an emaciated young man, 160 cm. in length. The skeleton was heavy, but there was no subcutaneous fat. The head was of the usual size and shape. The chest was long and deep, and the right side was more prominent than the left. The back showed no curvature. There was a recent surgical wound on the left where portions of several ribs had been resected, and the wound was gaping. There were no anomalies or deformities of importance. The skin was unusually pale. The hair of the head was dark brown. Rigor mortis was not present. There was no postmortem lividity. There was no discharge from the facial orifices.

On exploration through the wound, the left lung was found firmly adherent to the wall of the chest. This was freed with considerable difficulty, and the left lung was brought out through the wound. It weighed 600 Gm. There was a round operative wound 2 cm. in diameter and 6 cm. in depth. Both upper and lower lobes were considerably increased in density, and on section there was a large abscess cavity in each lobe. The cavity in the upper lobe was irregular but approximately 6 cm. in diameter. The lumen was partially filled with foul-smelling, grayish-brown, purulent material. The abscess in the lower lobe was 5 cm. in diameter and contained the same foul-smelling, purulent material. The tissue immediately about the abscesses was firm and grayish yellow.

The heart weighed 240 Gm. The chambers were practically empty. The valves were intact throughout. The base of the aorta was smooth and elastic.

The kidneys were removed because of the question of tuberculosis. The right kidney weighed 200 Gm.; the left, 190 Gm. The right kidney showed the calyces and pelvis markedly dilated. The calyces were lined by soft, yellow, caseous, purulent material. The cortex was of the usual thickness and showed normal dots and striae throughout. The left kidney was of the usual size. The capsule

stripped readily, leaving a smooth, unscarred, cortical surface. On section, the cortex ranged from 5 to 10 mm. in thickness. Dots and striae were readily made out. The pelvis was of usual size and was lined by smooth, intact epithelium. There was no evidence of tuberculosis.

COMMENT

When the patient was admitted to the hospital, the primary problem obviously was to evaluate the cause and extent of his paralysis. It was judged to be due to peripheral neuritis because of its distribution and its characterization by the loss of motor function, sensory changes and reflex signs. The etiologic agent was not so manifest. Four main causes were considered.

1. Lead was favored principally because of the patient's contact with white lead over a period of six years and the marked clinical similarity to lead neuritis with its marked motor and minor sensory manifestations. However, there was no evidence of lead absorption or intoxication and no excretion of lead in the urine or stools and none was present in the spinal fluid or the blood.

2. Tuberculosis as a cause of peripheral neuritis is rare, only a few cases having been reported. Crouzon and his associates [1] reported a case. Oppenheim [2] described a case of tuberculous myelitis producing symptoms similar to those in the case reported. Tuberculosis could not be definitely ruled out, except for its rarity and its more common association as a predisposing rather than a causative agent.

3. The pneumonia preceding the onset of the symptoms was considered as a possible cause because the infectious diseases, notably diphtheria, are known to produce polyneuritis.

4. The focal infection about the teeth and tonsils was considered as a possible cause, but was less likely than the foregoing infection.

The patient's exposure to lead in the past was considered to have given him a predisposition to polyneuritis, and it was probably precipitated by secondary infections as seen in the tonsils and teeth, supplemented by the tuberculosis. As the patient had harbored the tuberculous kidney for two years, it was decided to clear up all focal infection prior to a nephrectomy, and to this end dental extractions and tonsillectomy were performed, the latter being followed by the sequence of complications already described.

The occurrence of massive collapse of the lung following tonsillectomy is the first complication that I found reported in the literature.

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1. Crouzon, O.; Chavony, J. A.; Bertraud, I., and Froument: Tuberculous Polyneuritis, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:464 (March 28) 1924.

2. Oppenheim: Text Book of Nervous Diseases, London, T. Foulin, 1911.

The occurrence and diagnosis of this condition are now well known, having been first reported by Pasteur [3] in a series of cases following diphtheritic paralysis and in a later series following abdominal operations.[4] Bradford [5] then published a series of cases in which this condition followed gunshot wounds of the chest. Scrimger [6] reported the first cases in the American literature. Since them numbers of cases have been reported by Scott,[7] Elliot and Dingley,[8] Leopold,[9] Lund and Ritvo,[10] Jackson and Lee,[11] Smith and Davidson [12] and others.

The most excellent reviews of the subject have been published by Scott [7] and Leopold.[13] The preponderance of cases of massive collapse of the lung occur after abdominal operations and wounds of the chest. A few cases have been reported in which this complication occurred following nephrectomy and thyroidectomy. Regan [14] reported a case in which collapse occurred during the course of anterior poliomyelitis, and Kletz [15] reported one in which collapse occurred during the course of meningitis.

The mechanism of this phenomena is still in the controversial stage. The case reported would seem to support the view that there are a series of factors at work rather than any single one of those particularly advocated. The occurrence of the condition in a person already manifesting paralysis would indicate a possible primary involvement of the diaphragm and a secondary collapse of the lung, which view was originally held by Pasteur. The occurrence following tonsillectomy and the development of the infective complications point to an aspira-

3. Pasteur, William: Am. J. M. Sc. **100**:242, 1890.

4. Pasteur, William: Brit. J. Surg. **1**:587, 1914.

5. Bradford, John R.: Massive Collapse of the Lung, Quart. J. Med. **12**:127, 1919.

6. Scrimger, F. A. C.: Surg. Gynec. Obst. **32**:486 (June) 1921.

7. Scott, W. J. M.: Postoperative Massive Collapse of the Lung, Arch. Surg. **10**:73 (Jan.) 1925.

8. Elliot, T. R., and Dingley, L. A.: Massive Collapse of Lung Following Abdominal Operations, Lancet **1**:1305, 1914.

9. Leopold, S. S.: Post-Operative Massive Pulmonary Atelectasis and Drowned Lung, Am. J. M. Sc. **167**:421, 1924.

10. Lund, C. C., and Ritvo, Max: Post-Operative Massive Collapse of the Lung, Boston M. & S. J. **190**:1103, 1924.

11. Jackson, C., and Lee, W. D.: Acute Massive Collapse of the Lungs, Ann. Surg. **82**:364, 1925.

12. Smith, F. J., and Davidson, E. C.: Post-Operative Pulmonary Atelectasis, J. Michigan M. Soc. **26**:295, 1927.

13. Leopold, S. S.: Massive Collapse of the Lung: Bedside Diagnosis (Blumer), Philadelphia, W. B. Saunders Company, 1928.

14. Regan, J. C.: Massive Collapse of the Lung in Acute Poliomyelitis, Lancet **2**:1222, 1924.

15. Kletz, N.: Massive Collapse of the Lung Complicating Acute Meningitis, Lancet **1**:179, 1927.

tion of infective material plugging the bronchi and a secondary collapse of the lung, as maintained by Jackson and Lee. This case is no obvious contribution in favor of the later theory of a reflex mechanism involving the bronchoconstrictor and dilator fibers of the vagus. However, one would be inclined to favor Scott's view that massive collapse does not arise from one particular cause, but consists of a chain of events initiated as a primary nerve reflex, causing bilateral partial obstruction in the peripheral system, plus such secondary factors as position, tenacious secretion or infection, which make the obstruction complete on one side in advance of that on the other. A hyperventilation on the opposite side keeps the passages open. Then the air on the occluded side is absorbed in a few hours, and the complete picture develops.

The clearing of the neurologic manifestations in the presence of a continued tuberculous focus and while the patient was subjected to the exceedingly toxic effects of pneumonia was the most unusual aspect of the case. This would seem to mitigate against tuberculosis as a causative factor, because it was still present; against lead because no evidence of lead absorption was found and no deleading process was carried out, and against pneumonia because improvement occurred in the presence of a second pneumonic process. Conversely, it would seem to favor focal infection as the etiologic agent, as improvement occurred following the removal of focal infection. The latter would seem to be the most satisfactory explanation. An interesting speculation arises as to whether a repetition of the massive collapse of the lung would occur if a nephrectomy were performed, a reaction that occurred in a case reported by Scott after subsequent nephrectomies and by Farrar after subsequent laparotomies, the occurrence of which is adduced as supportive evidence in favor of the neurogenic theory of causation, these persons being thought to have a predisposition to massive atelectasis.

SUMMARY

The history and course of a case of peripheral neuritis with paralysis are submitted. The etiology of this case still presents interesting speculation. The interesting features of the case were the clearing up of the paralysis following the removal of focal infection and the occurrence of massive collapse of the lung following tonsillectomy.

CARCINOMATOUS DEGENERATION OF POLYP OF THE STOMACH

REPORT OF EIGHT PERSONAL CASES WITH A REVIEW OF TWENTY-FOUR RECORDED BY OTHERS *

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Polyp of the stomach is of clinical importance chiefly because of its tendency to undergo malignant degeneration; it is important also because of its tendency, whether benign or malignant, to give rise to hemorrhage and to pyloric obstruction. In a group of eight cases of carcinomatous gastric polyp that we have observed during the past ten years, three patients had experienced gastric hemorrhage of such a degree as to lead to a preliminary diagnosis of primary anemia, and all but one had developed pyloric stenosis. These three phenomena—malignancy, hemorrhage and obstruction—may be looked on as the important consequences of gastric polyp, but it is to carcinomatous transformation particularly that we wish to direct attention at this time.

Under the heading of benign polyp of the stomach is included, strictly speaking, all the nonmalignant intragastric pedunculated tumors; but, since the myoma, the fibroma, the angioma, the lipoma and the myxoma are only rarely pedunculated and have not been encountered in our group of cases, they are excluded from this report. Reference is made, therefore, only to those of an adenomatous nature, which, because of their epithelial structure, when malignant show carcinomatous change.

In addition to our personal series of eight cases of carcinomatous gastric polyp, a group of twenty-four has been collected from the literature. To one making a hurried review, it may seem that many more cases have been reported. This is due to the fact that certain authors have not differentiated clearly between polyps of the stomach and those of other portions of the digestive tract; furthermore, some of them have not distinguished between polyps that were themselves malignant and polyps associated with malignancy elsewhere in the stomach. Also, interstitial benign tumors, such as myoma and fibroma, which undergo sar-

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comatous change and which do not usually produce true intragastric polyps, have sometimes been included.

The accumulated data on these two groups of cases will be presented separately, since the diagnostic study has been more complete in our personal series, but so far as the investigations made and recorded in the two groups have corresponded, it will be noted that the observations have been quite similar. Each of the thirty-two cases showed carcinoma of at least one intragastric polyp, and evidence will be adduced to indicate that the primary lesions were benign adenomatous polyps.

INCIDENCE

The incidence of polyp of the stomach, whether benign or malignant, is difficult to determine at the present time. This is due largely to the fact that until recently preoperative clinical diagnosis was impossible; also, at operation, unless specially considered, a polyp is easily overlooked, and at autopsy, if a secondary malignant process has occurred, it may be so extensive as to obscure the nature of the primary lesion. Today, however, with improvement in roentgenologic technic, the diagnosis may be made quite early, even before symptoms or any of the complications have occurred, and consequently it may be expected that in the future the incidence of the disease may be more accurately indicated.

That gastric polyp is not rare is shown by the fact that two of us (Eliason and Wright [1]), in 1925, were able to collect 610 cases of primarily benign gastric tumors, including 560 from the literature and 50 from the surgical and autopsy records of this and the Philadelphia General Hospitals (8,000 autopsy records reviewed). Of this total number, it is impossible to say how many patients had pedunculated tumors, but of our 50 cases, 35, or 70 per cent, showed polyps. Since that time, 6 other cases of polyp have been observed. Of this total of 41 cases of gastric polyp, including 9 that have been operated on by one of us (E. L. E.), 23 supplied specimens that were subjected to careful microscopic study, and of this number 8, or 35 per cent, showed carcinomatous change.

In referring to polyps of the entire digestive tract, and not merely to those of the stomach, Wechselman [2] stated that from 50 to 60 per cent become malignant, and Doering [3] gave the percentage figure as 46. Muehlengracht [4] agreed that one half or more of intestinal polyps under-

1. Eliason, E. L., and Wright, V. W. M.: Benign Tumors of the Stomach, Surg. Gynec. Obst. **41**:461 (Oct.) 1925.

2. Wechselman, L.: Polyp und Carcinom im Magen-Darmkanal, Beitr. z. klin. Chir. **70**:855, 1910.

3. Doering, H.: Die Polyposis intestini und ihre Beziehung zur carcinomatösen Degeneration, Arch. f. klin. Chir. **83**:194, 1907.

4. Muehlengracht, E.: Ueber die Gastritis polyposa, Virchows Arch. f. path. Anat. **214**:438, 1913.

goes malignant degeneration, but insisted that such change in the lesions located in the stomach is rare. Mills [5] found evidence of malignancy in 20 per cent of twenty collected cases of gastric polyp, and Brunn and Pearl [6] in 12 per cent of their eighty-four cases, while Balfour and Henderson [7] found such degenerative change in only 3.5 per cent. Stewart,[8] in forty-seven cases of gastric polyp encountered in 11,000 necropsies, discovered associated carcinoma in thirteen, but in only three (6.4 per cent) could it be determined that the malignant process had originated in a polyp. In defense of our somewhat higher percentage figure, it may be stated that sometimes only one of several polyps in a single case showed the malignant change, and that, because of our interest in the exact diagnosis, an extensive search of many sections was made in each instance.

The significance of gastric polyp may be appreciated if the number undergoing malignant change is considered in relation to the total number of cases of gastric carcinoma. For instance, our 8 cases have been found in a series of about 200 operations for cancer of the stomach, thus constituting approximately 4 per cent of the group. Stewart [8] had 13 cases of gastric carcinoma that were probably secondary to adenomatous polyp, all at least being associated with such polyps, in 263 cases of gastric cancer, about 5 per cent. This approximates the percentage of cases of carcinoma occurring on an ulcer basis. Thus, as Hurst [9] has suggested, adenomatous polyp, like ulcer and chronic gastritis, may be looked on as a precursor of carcinoma of the stomach.

The relatively large number of our malignant cases, encountered in a single hospital within a decade, in comparison with the number that we have been able to collect from the literature, suggests that insufficient attention has been given to this subgroup of gastric cancer and to this important and frequent complication of gastric polyp.

PERSONAL CASES

Case 1.—F. A. D.,[10] an American, a white man, aged 31, was admitted to the hospital on Nov. 12, 1919, because of epigastric pain and anorexia from which

5. Mills, G. P.: Multiple Polypi of the Stomach (Gastritis Polyposa): With the Report of a Case, Brit. J. Surg. **10**:226 (Oct.) 1922.

6. Brunn, H., and Pearl, F.: Diffuse Gastric Polyposis-Adenopapillomatosis Gastrica, Surg. Gynec. Obst. **43**:559 (Nov.) 1926.

7. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Stomach, Ann. Surg. **85**:354 (March) 1927.

8. Stewart, M. J.: The Relation of Malignant Disease to Benign Tumours of the Intestinal Tract, Brit. M. J. **2**:567 (Sept. 28) 1929.

9. Hurst, A. F.: Precursors of Carcinoma of the Stomach, Lancet **2**:1023 (Nov. 16) 1929.

10. Reported in full by Miller, T. G.: Polypoid Carcinoma of the Stomach, J. A. M. A. **76**:229 (Jan. 22) 1921.

he had suffered for a period of three weeks. Eighteen months previously, as a soldier, he had been studied in the United States Base Hospital at Camp Meade on the service of Dr. Nellis B. Foster, and at that time his disease had been diagnosed as primary pernicious anemia (red blood cells, 1,000,000; hemoglobin, 40 per cent). No gastric analysis and no examination of the stool were reported. Five transfusions of blood, 300 cc. each, were given. He made a good symptomatic recovery, and subsequent blood studies were normal.

On examination in November, 1919, a hard, tender and movable mass about the size of a lemon was felt under the right costal margin just to the right of the xiphoid. Peristaltic waves were visible, and as certain ones reached the median line the stethoscope revealed a distinct squirting sound. A small, firm, freely movable gland just above the inner end of the left clavicle was palpable. Blood counts and the hemoglobin estimation were within normal limits. Repeated gastric analyses showed achlorhydria. The feces showed a trace of occult blood on one occasion, the examinations of other stools for blood being negative. The Wassermann reaction was negative.

Roentgenologic study showed an almost complete gastric residue six hours after a barium sulphate meal, marked hyperperistalsis with deep segmenting waves, the waves coursing along the curvatures without interference, and just above the greater curvature in its most dependent part a large, clear area about the size of a silver dollar. The serial exposures showed a constant vacuole defect strongly suggesting duodenal ulcer. It was concluded that pyloric obstruction was present, probably of duodenal origin, and that the gastric defect was probably due to a papilloma, possibly malignant.

At operation by Dr. John B. Deaver, a gastrotomy revealed a rounded, polypoid mass about the size of a walnut attached by a pedicle to the mucous membrane along the greater curvature. The muscle coats did not seem to be involved. The mass that had been palpated at the bedside was found to be a secondary lesion attached to the edge of the liver. Dense adhesions involved the gallbladder and duodenal bulb and explained the duodenal deformity noted on roentgenologic study. Glandular metastatic lesions were also observed.

The intragastric mass was excised and is described completely, with illustrations, in the original report of this case. It showed a malignant papillomatous portion, a simplex portion and a scirrhous portion. Some ulceration was noted over the free surface of the tumor.

The patient died about three weeks after the operation, and autopsy was not obtained.

Case 2.—E. K.,[11] a man, aged 45, had been without symptoms of any sort until about three months before his admission to the hospital on April 30, 1923, when he first became aware of epigastric discomfort, and later of a gnawing epigastric pain before meals. Ingestion of the softer foods, especially milk, gave relief, whereas the coarser foods increased the pain. On two occasions the pain had been very severe. He had lost 40 pounds (18.1 Kg.), his best weight being 220 pounds (99.7 Kg.). Blood-streaked material had been vomited twice. He had been in the habit of taking whisky before each meal. He gave a history of stone in the bladder ten years previously.

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11. Reported previously as case 1 by Eliason, E. L.; Pendergrass, E. P., and Wright, V. W. M.: The Roentgenological Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through the Pylorus, Am. J. Roentgenol. **15**:295 (April) 1926.

Physicial examination revealed only some tenderness in the epigastrium, the edge of the liver palpable, dental caries and ragged tonsils. His blood pressure was 152 systolic and 100 diastolic. The red blood cells numbered 4,300,000, and the leukocytes, 10,000. The hemoglobin percentage was 81. Urinalysis gave negative results. The feces showed occult blood. The Wassermann reaction of the blood was negative. Fractional gastric analysis revealed achlorhydria; this was confirmed by three subsequent analyses.

On three occasions, while under observation, he had attacks of severe epigastric pain, one of these attacks requiring morphine for relief. Although roentgenologic renal study revealed a stone in the pelvis of the right kidney, the location of the pain was such as to suggest that it was gastric rather than renal in origin.

Roentgenologic study of the gastro-intestinal tract showed moderate gastric residue, intermittent hyperperistalsis, hypermotility at times (usually less than commensurate with the peristalsis), pyloric spasm or obstruction and a defect of the duodenal bulb, producing almost complete obliteration of this portion of the duodenum. The diagnosis of the roentgenologist was duodenal ulcer or adhesions.

On May 16, an exploratory laparotomy by one of us (E. L. E.) revealed only a gastric polyp and some duodenal adhesions. A gastrotomy was performed, and the polyp, which was found attached to the posterior wall of the stomach near the pylorus, was excised. The patient died on the following day. Autopsy disclosed an additional and extensive lesion high up on the posterior aspect of the fundus of the stomach, which had not been observed at operation, and which proved to be carcinomatous. Microscopic study of the polyp, removed at operation, showed it to be a papilloma that also was undergoing carcinomatous change.

Review of the roentgenologic films in this case disclosed a circular central defect in the duodenal bulb (fig. 1), which was due undoubtedly to protrusion of the polyp through the pylorus, since autopsy showed the pylorus to be wide open, and no other explanation for such a defect was suggested. Since that time such defects have led to a correct diagnosis, as subsequent cases will illustrate.

Case 3.—G. L.,[12] a Negro, a day laborer, at the age of 39 was first admitted to the medical service of the Presbyterian Hospital, of Philadelphia, on Dec. 26, 1917, stating that for two months he had been having gnawing pains in the region of the stomach. They usually appeared soon after eating, but sometimes several hours after a meal. Heavy foods especially seemed to produce the pains. He had lost some weight, but had not vomited. He showed considerable emaciation, and the abdomen was distended, tympanitic and without palpable masses.

A tentative diagnosis of carcinoma of the stomach was made, and operation advised. This was refused, but finally the patient was discharged greatly improved. In 1920, he was readmitted to the Presbyterian Hospital and operated on, the stomach and duodenum being reported as normal. At that operation his appendix was removed, and some adhesions about the gallbladder were freed. Subsequently he was observed in our outpatient medical dispensary, and repeated gastric analyses over a three year period constantly showed achlorhydria. Repeated Wassermann tests gave negative results.

He was admitted to our medical wards on Jan. 25, 1924, still complaining of abdominal pains, now of an aching character, more or less constant and increased by activity. He had lost from 20 to 30 pounds (9 to 13.6 Kg.). Another fractional gastric analysis showed achlorhydria. Blood studies, including another Wassermann test, gave negative results.

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12. This case also was reported previously, as case 2, by Eliason, E. L.: Pendergrass, E. P., and Wright, V. W. M.: Am. J. Roentgenol **15**:295 (April) 1926.

At this time roentgenologic study showed no gastric residue, normal peristalsis, slightly increased motility and a constant vacant area in the antrum pylori (fig. 2). A diagnosis of papilloma or nodular carcinoma in the pyloric region was made.

Operation by one of us (E. L. E.) on Feb. 13, 1924, revealed a small lump on the posterior wall of the stomach, which could be pushed along the lumen of the organ toward the pylorus. Gastrotomy was then performed, and the affected area of the posterior wall was pushed out through the opening, displaying three polyps,

Fig. 1 (case 2).—Serial roentgenograms, viewed from behind, showing the constant circular defect of the first portion of the duodenum. Roentgenologic diagnosis: duodenal ulcer or adhesions (1923).

one the size of a cherry and the other two much smaller.[13] Each had a separate pedicle. The polyps were excised. The patient made a good recovery, except for a slight attack of bronchitis, and was discharged a month later.

13. See the illustrations included in the original article.

Three months later he had a recurrence of his abdominal pain which has persisted since that time. On Feb. 26, 1925, he was readmitted to the medical wards for roentgenologic study, which showed no residue, good peristalsis and motility and defects suggestive of perigastric adhesions. No evidence of a recurrence of the polyps was made out.

Since then he has been under observation in the gastro-intestinal clinic. His pain has varied, usually being less severe, and his weight has increased. He has

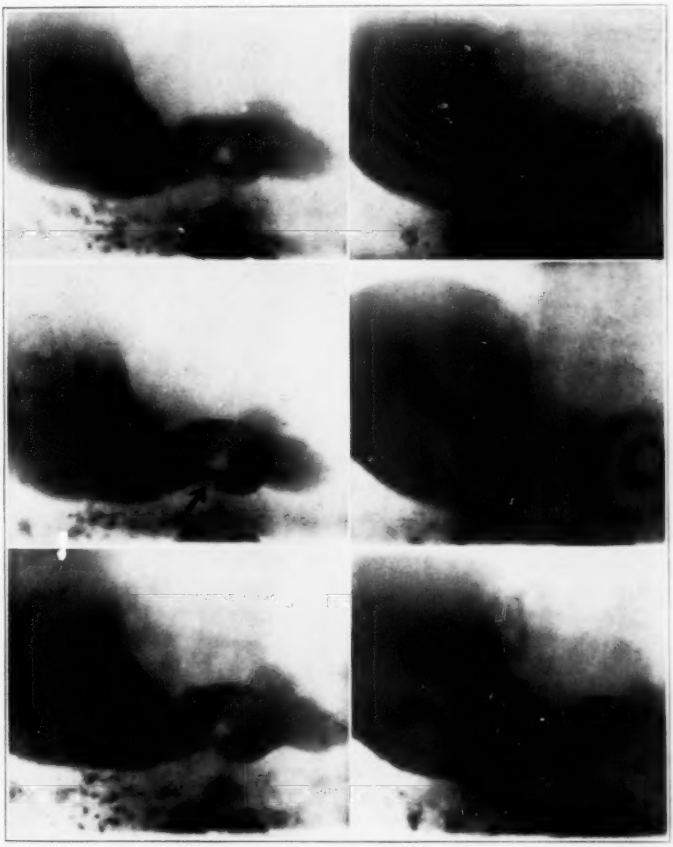

Fig. 2 (case 3).—Serial roentgenograms, viewed from behind, showing the constant area of decreased density in the pyloric antrum. Roentgenologic diagnosis: papilloma or nodular carcinoma (1924).

been able to resume work as a night watchman. Two more fractional gastric analyses have showed the same achlorhydria. Another gastro-intestinal roentgen study on Dec. 1, 1926, showed no residue, normal peristalsis in the distal third of the stomach, increased motility and some irregularity in the outline of the stomach

suggesting only adhesions. A repetition of this examination two weeks later gave the same results.

The large polyp removed from the stomach in 1924 proved to be an adenoma undergoing malignant change.

Case 4.—J. M., a man, an interior decorator, aged 45, became a private patient of one of us (T. G. M.) on Sept. 27, 1927, and stated that he had been without

Fig. 3 (case 4).—Serial roentgenograms, viewed from behind, showing a large defect in the pyloric region and the lower third of the stomach; also a large basal deformity of the duodenal cap. Roentgenologic diagnosis: probable carcinoma (1927).

symptoms of any kind until three weeks previously. At that time, after a heavy meal, he had become nauseated and had vomited. Subsequently he had had almost constant epigastric distress with eructations, a sense of abdominal distention and, irregularly, nausea and vomiting. He had not had any severe pain. He had lost

15 pounds (6.8 Kg.) during the three weeks. His past medical history was negative. His mother had died of carcinoma of the breast. He had been under considerable strain because of business difficulties and because of the illness of his wife, who had exophthalmic goiter. Two children were in good health.

Physical examination revealed only some carious teeth with pyorrhea, evidence of the loss of weight and a little soreness in the epigastrium. Urinalysis and the usual examinations of the blood gave negative results. The Wassermann reaction

Fig. 4 (case 4).—Photograph of the specimen removed at operation, showing the thickened gastric wall and polyp on the posterior wall near the pylorus.

of the blood was negative. A gastric analysis indicated marked gastric retention and achlorhydria. The blood pressure was 155 systolic and 105 diastolic.

Roentgenologic study showed a complete gastric residue after six hours, no peristalsis and only slight motility on one occasion. A large defect in the pyloric region and the lower third of the stomach and a constant basal deformity of the duodenal cap were noted (fig. 3). The roentgenologist's diagnosis was probable carcinoma of the pyloric end of the stomach, with a syphilitic lesion as a possibility. It was suspected that the duodenal deformity was due to the gastric lesion.

At operation, on Oct. 26, 1927, by one of us (E. L. E.), the pylorus was found to be quite hard and suggestive of carcinoma. The induration involved the entire circumference of the wall of the stomach and extended upward for 3 inches (7.6 cm.) beyond the pylorus. A nodular piece of tissue was palpated in the duodenal cap, and it was slipped back into the stomach without opening the latter organ. A few small nodules in the lesser omentum were noted. A subtotal gastrectomy with the Polya type of anastomosis was performed. Although the

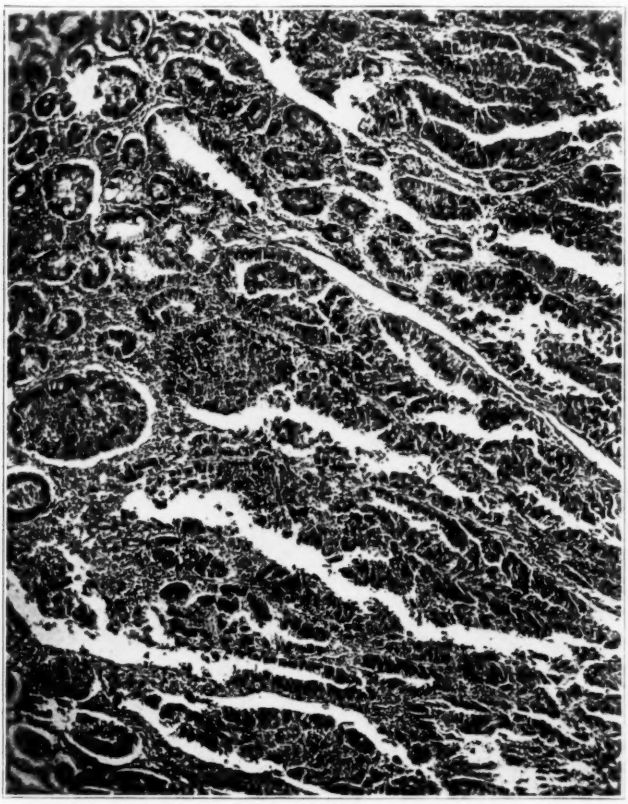

Fig. 5 (case 4).—Photomicrograph, showing adenocarcinomatous changes in the polyp.

immediate convalescence was somewhat stormy, the patient left the hospital on November 15, and a month later was gaining weight, had a good appetite and complained only of diarrhea when he did not keep to a strictly starchy diet. He returned to his work, felt as well as ever and in May, 1928, was back to his usual weight.

A second roentgen study in the following month showed no filling defects, no gastric residue, a stomach of the size and shape of an orange and an occasional

spurt of contents into the jejunum by tonic contraction of the wall of the stomach. During the following February (1929), however, symptoms indicative of gastric obstruction again developed, he lost weight and strength rapidly and died on March 7, presumably of an extensive recurrence of his primary lesion. Autopsy was not obtained.

The specimen removed at operation consisted of the lower third or half of the stomach. Throughout all but the free borders of it, much thickening and

Fig. 6 (case 4).—Photomicrograph from the stomach near the abscess at the base of the polyp, showing adenocarcinoma with marked round cell infiltration.

induration were present, and attached by a pedicle to the posterior wall was a polyp that measured 3.5 cm. in diameter (fig. 4). An abscess was found at the base of the polyp. Microscopic sections showed: (1) adenocarcinoma of the polyp and (2) chronic inflammatory changes in the wall of the stomach, with malignant change in certain areas (figs. 5 and 6).

CASE 5.—A. M., the only woman in our series, aged 61, was admitted to the gastro-intestinal clinic on Oct. 6, 1927, complaining of diarrhea. She had been

having from three to six bowel movements daily for six years, but was otherwise in good health until about six months previously, when she noted some dizziness on stooping; occasionally she would fall during such attacks. Two months before admission, and following the eating of steamed clams, definite diarrhea developed associated with colicky pain in the abdomen. From that time until her admission she had had from five to twenty movements a day, liquid, gray or yellow, containing considerable mucus. The pain did not persist. Blood was observed in the stools on several occasions, but the amount was not large. The fecal evacuations were particularly frequent immediately after eating. She was not specially weakened by the diarrhea, but when first seen she was 25 pounds (11.3 Kg.) below her average weight. Her appetite was impaired, but there had been no nausea or vomiting.

She had had malaria at the age of 31, and had passed through her menopause at 40 without special symptoms. Her husband had died thirty-five years previously, and her only child, a daughter of 40, was living and in good health. Her habits were excellent.

Physical examination showed her to be fairly well developed and nourished, weighing 116 pounds (52.6 Kg.). No focal infections were found. The abdomen was soft and slightly distended and presented some tenderness to deep pressure over the cecal area and in the upper left quadrant. No other physical abnormalities were discovered.

On October 8, a simple test meal showed no free hydrochloric acid and a total acidity of 25. The amount of gastric contents removed at the end of forty-five minutes was 100 cc. The occult blood test gave positive results. A fractional gastric analysis showed no free hydrochloric acid in any of the specimens, but occult blood was constantly present. The Wassermann reaction of the blood was negative.

Proctoscopic examination showed a small polyp, about one-half the size of an olive, springing from the anterior wall of the rectum about 4 inches (10.16 cm.) above the anus. The surface of this was smooth and of normal color, and did not bleed when touched. Otherwise, the results of the examination were negative. Examination of the feces by Dr. Frank B. Lynch, Jr., showed no parasites or ova, many pieces of undigested vegetable material and a positive occult blood test. Several subsequent examinations of the feces gave similar results. A Gram stain showed an excess of gram-negative organisms.

Gastro-intestinal roentgenologic study showed a marked gastric residue, the stomach being J-shaped and atonic with the greater curvature about 1 inch (2.5 cm.) below the level of the iliac crests. Continual hyperperistalsis was observed, but the waves were not numerous; they moved slowly, and were deep and segmenting. Motility was commensurate. The waves started in the fundus and progressed to the pylorus without interference. The films of the stomach indicated a lesion involving the greater curvature, which was interpreted as probably due to carcinoma (fig. 7). A barium enema study gave negative results.

The patient was admitted to one of the medical wards for study and observation on October 24, but nothing new was noted. Finally, on November 28, surgical exploration of the abdomen by one of us (E. L. E.) disclosed a mass at the junction of the middle and lower thirds of the stomach. It did not seem to be attached to all the coats of the wall of the stomach, since at least the outer coat could be moved over it on all sides, and a large polyp was suspected. A sleeve resection of the stomach without preliminary gastrotomy was performed. The patient made an uneventful recovery from the operation, except for the development of a few pus pockets in the wound, and was discharged on Jan. 9, 1928.

On February 14, her weight was only 111 pounds (50.3 Kg.) in spite of the development of peripheral edema, and she was quite weak, but the diarrhea had disappeared. Soon afterward she began to improve in every way, and on March 7, a roentgenologic examination showed only a slight gastric residue and a progression of the peristaltic waves from the fundus to the pylorus with an occasional antiperistaltic wave. It was concluded that the stomach was functioning satisfactorily.

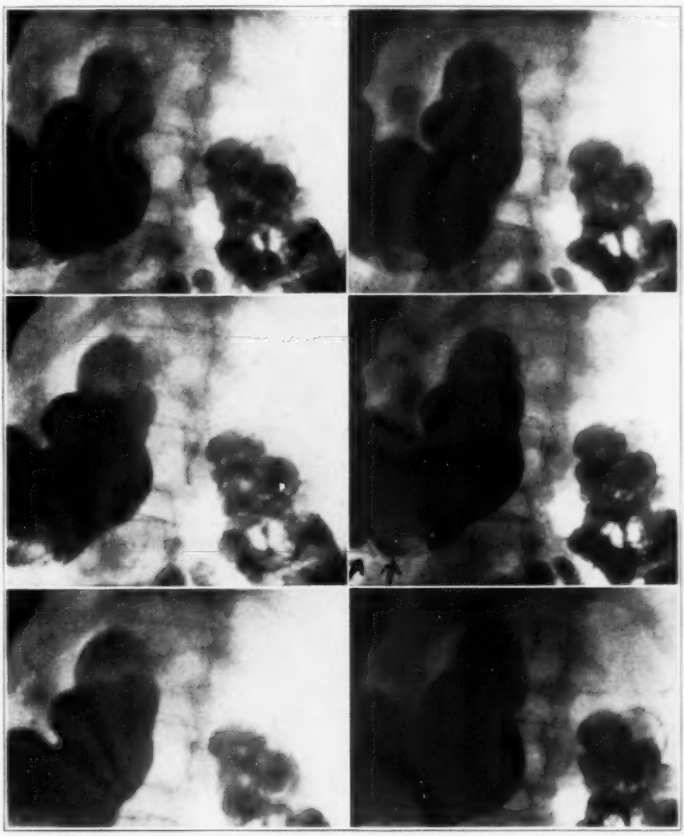

Fig. 7 (case 5).—Serial roentgenograms, viewed from behind, showing a constant defect along the greater curvature of the stomach. Roentgenologic diagnosis: probable carcinoma (1927).

She had gained 7 pounds (3.2 Kg.) by June 5, and on March 5, 1929, weighed 137½ pounds (62.3 Kg.), 21½ pounds (9.8 Kg.) more than before her operation. No edema was present at that time, and she had no complaints except that she was too stout. By November, however, a fixed mass had developed in the left lower

quadrant of the abdomen; the liver was enlarged and irregular. Her weight was decreasing. It was believed that an extensive recurrence of cancer had developed.

The specimen removed (fig. 8) showed three polyps on its mucosal surface, each being attached by a separate pedicle. The largest one measured 6 by 3.5 by 3 cm. and each of the others about 1 cm. in diameter. All of the lesions were soft, friable and hemorrhagic. Microscopic sections showed that one was probably a benign adenoma and one an adenocarcinoma, and that one was undergoing early malignant change (figs. 9, 10 and 11).

Fig. 8 (case 5).—Photograph of the specimen removed at operation, showing three polyps.

CASE 6.—H. C., a fish dealer, aged 47, a private patient of Dr. Alfred Stengel, was admitted to our medical wards on Oct. 19, 1927. He had been in good health until two years previously when, following his wife's death, anorexia and gaseous eructations developed; later, pallor and loss in weight (22 pounds [10 Kg.] in the two years) were noted. Six weeks before admission he had to give up his work on account of weakness, headache, dyspnea, palpitations and paresthesia of the extremities.

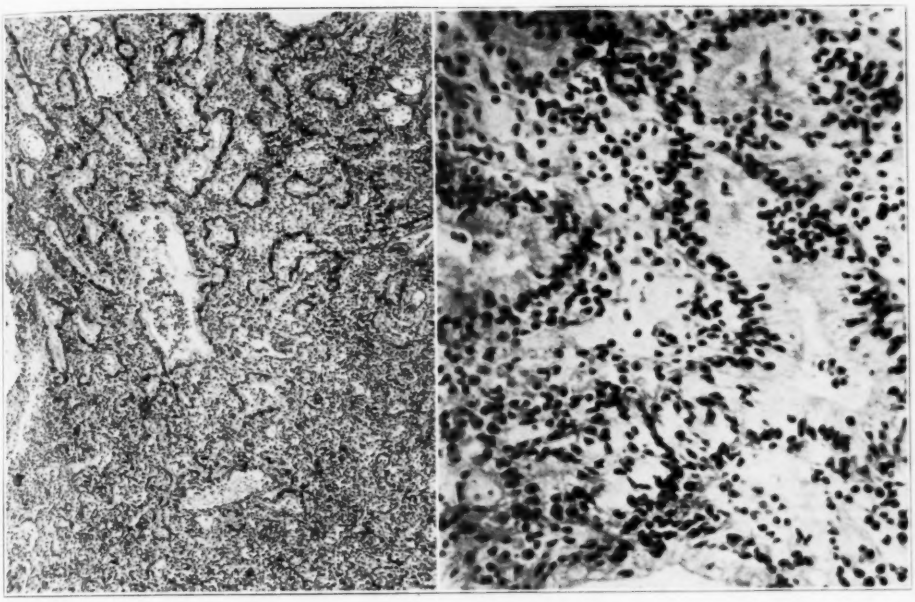

Fig. 9 (case 5).—Low and high power photomicrographs of smallest polyp, showing adenoma, probably benign.

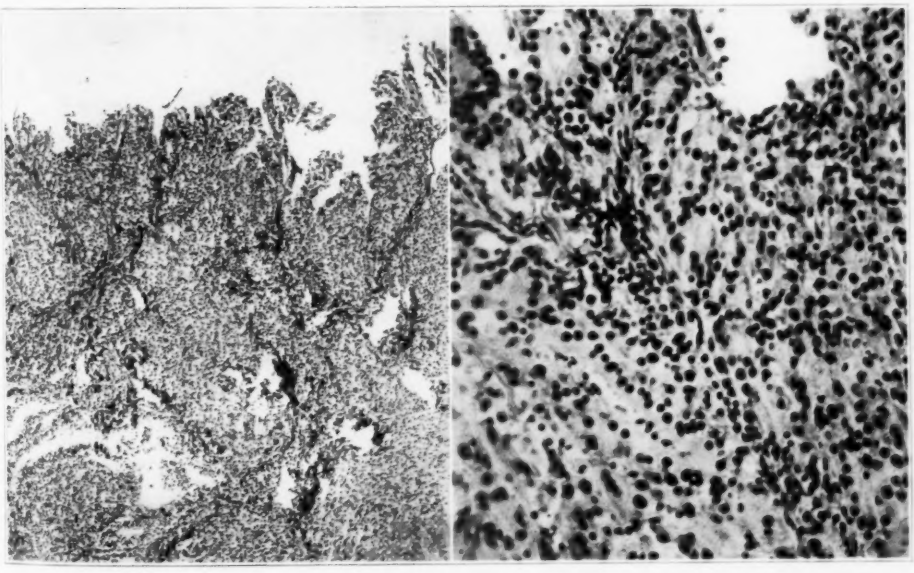

Fig. 10 (case 5).—Low and high power photomicrographs from the largest polyp, showing adenocarcinoma.

Physical examination showed marked pallor of the skin and mucous membranes, some atrophy of the tongue, a systolic apical heart murmur, a vague epigastric mass, a questionable Ewald gland and some uncertain sensory changes in the legs. The red blood cells numbered 2,800,000 and the leukocytes, 12,200, and the hemoglobin percentage was 30. Nucleated red cells were found. The van den Bergh test gave negative results. The blood platelets numbered 272,000, and the reticulated red blood cells amounted to 3.5 per cent. A blood culture was negative. Fractional gastric analysis, with and without histamine, showed achlorhydria. The feces, on a meat-free diet, were positive for occult blood. The Wassermann reaction of the blood serum was negative.

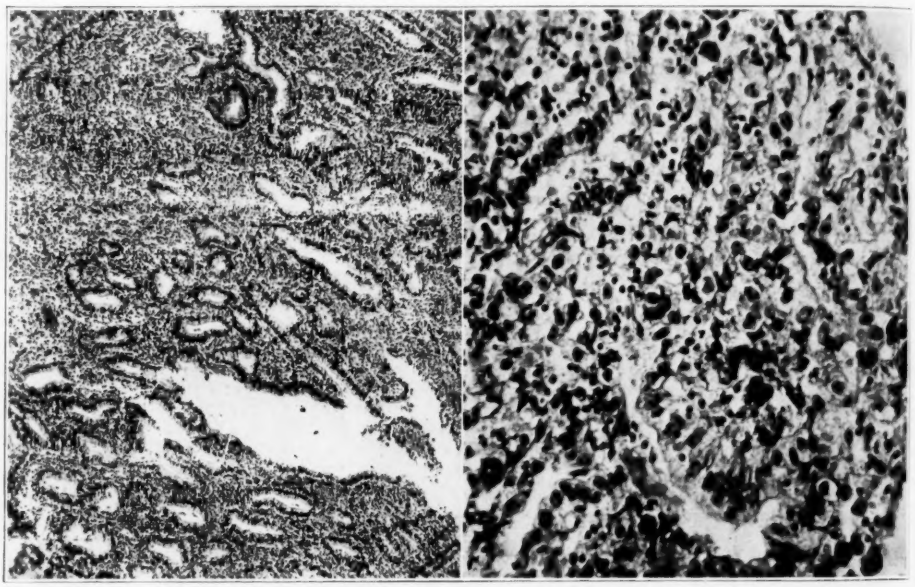

Fig. 11 (case 5).—Low and high power photomicrographs from the intermediate-sized polyp, showing early malignant degeneration.

He had some fever, and a subacute endocarditis was considered. This was later abandoned for a diagnosis of primary pernicious anemia. The possibility of a gastric polyp with malignant change was also suggested.

Roentgenologic investigation of the gastro-intestinal tract showed a marked gastric residue, normal peristalsis and motility and a large filling defect along the greater curvature of the stomach at its middle portion (fig. 12). In spite of the defect, the peristaltic waves progressed to the pylorus without interference. The roentgenologic diagnosis was a large carcinoma or a benign tumor along the greater gastric curvature.

Following two transfusions of blood, 350 cc. each, one of us (E. L. E.), at operation on November 2, found a large cakelike mass in the stomach, apparently having a crater and apparently attached to the posterior wall near the greater

curvature. It gave the impression of being a polyp. A subtotal gastrectomy with the Polya type of anastomosis was performed. One subsequent transfusion of 500 cc. of blood was administered, and the patient made a good recovery, being discharged on November 28, though still anemic (hemoglobin, 43 per cent).

His weakness persisted; he became aware of some difficulty in swallowing food, and epigastric pain developed, which he had not had previous to the operation.

Fig. 12 (case 6).—Roentgenogram, viewed from behind, showing the large filling defect along the greater curvature. Roentgenologic diagnosis: large carcinoma of the stomach or a benign polyp (1927).

On March 8, 1928, reexamination of the digestive tract by the roentgen rays showed an obstacle to swallowing at the lower end of the esophagus, and suggested some infiltration of the gastric wall and a new growth in the fundus of the stomach. A review of the films made at the original examination then showed evidence of such a fundal lesion that had not been appreciated previously.

On June 26, when last seen, he had lost 16 pounds (7.3 Kg.) since his operation, was vomiting everything he tried to swallow and was rapidly losing ground. It was believed that he had an extensive carcinomatous involvement. He died at his home a few weeks later, and autopsy was not obtained.

The specimen removed at operation consisted of the lower half of the stomach, and presented a large flattened polyp (fig. 13) attached to the posterior wall by a fairly firm stalk. The tumor mass measured 8 cm. in diameter and, on microscopic study, proved to be a medullary carcinoma (fig. 14).

Fig. 13 (case 6).—Photograph of the specimen removed at operation, showing a large flattened polyp.

Case 7.—W. C. H., an Englishman, resident in the United States for twenty-three years, aged 44, a master mechanic, became a private patient of one of us (T. G. M.) on July 2, 1928. Six months previously he had noted that his feces were black, and from that time had felt distinctly below par. He had had no definite gastric symptoms, except that when late for a meal he often felt unduly hungry. One day in early June, anorexia and fleeting abdominal pains developed. That evening he became nauseated and vomited several pints of chocolate-colored fluid with blood clots, subsequently having tarry stools. After ten days in bed,

under the observation of a local physician, he returned to his work, but on June 30, he suffered from much dizziness and increasing weakness, with a return of blood in the stools, and was forced back to bed. He had lost 7 pounds (3.2 Kg.).

Physical examination showed only some tenderness just to the left and below the umbilicus. No masses were felt. No pallor or other signs of shock were observed. The red blood cells numbered 4,000,000, and the hemoglobin amounted to 80 per cent. The leukocytes numbered 5,000, and the differential count was normal. The feces showed no blood grossly, but the test for occult blood was

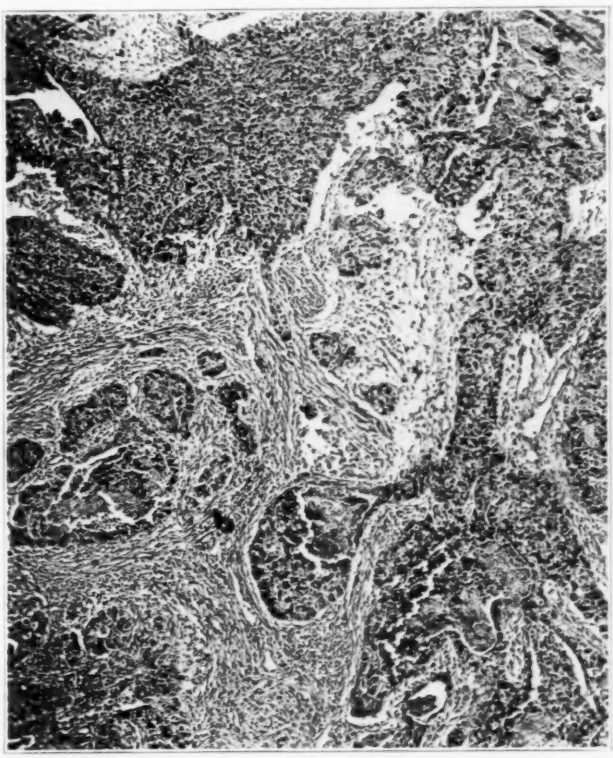

Fig. 14 (case 6).—Low power photomicrograph of polyp, showing medullary carcinomatous changes.

positive. A fractional gastric analysis, cautiously done on the following day, revealed a complete absence of free hydrochloric acid; this was later confirmed by a histamine test. The Wassermann reaction was negative. The blood pressure was 98 systolic and 75 diastolic. On July 16, after two weeks' rest and the Andresen diet for gastric hemorrhage, roentgenologic study of the gastro-intestinal tract showed a moderate gastric residue, hypoperistalsis and hypomotility of the stomach and a large pyloric defect which interfered with the peristaltic waves,

produced obstruction and seemed to project into the duodenal cap (fig. 15). The roentgenologist's diagnosis was a carcinoma or a large polyp of the pyloric end of the stomach.

Operation by one of us (E. L. E.) two days later revealed at once a gastric polyp that could be pushed back and forth through the pyloric ring. When the stomach was opened, two nodular and ulcerated masses were seen attached to the

Fig. 15 (case 7).—Serial roentgenograms, viewed from in front, showing a marked filling defect of the pylorus with extension into the duodenal cap. Roentgenologic diagnosis: carcinoma or large polyp of the pyloric end of the stomach (1928).

posterior gastric wall near the pylorus. The smaller one of these could easily reach and enter the duodenum. On gross inspection, neither of the polyps suggested malignant degeneration, but a gastroscope revealed a single, whitish, indurated plaque higher in the stomach, which strongly suggested malignant change. A single

hard node was felt in the omentum. Accordingly, a subtotal gastrectomy with Polya anastomosis was performed.

A good recovery was accomplished, and the patient left the hospital on August 15.

On Feb. 23, 1929, he reported that he had been back at work since early September, that his appetite was good and that with frequent small feedings he was gaining weight steadily. His weight was then half a pound (0.2 Kg.) greater than on July 2, 1928. He had no abdominal symptoms.

Fig. 16 (case 7).—Photograph of the specimen removed at operation, showing polyps. One of the polyps could easily be pushed beyond the line of the pyloric ring.

On Aug. 5, 1929, he weighed 137 pounds (62.1 Kg.), which was his normal weight. He had no symptoms, and had been working steadily. He was eating three regular meals daily, his appetite being good at all times. Physical examination of the abdomen gave negative results.

The specimen removed consisted of the lower third of the stomach with a small portion of the duodenum (fig. 16). The two polyps were attached to the posterior wall by pedicles, the largest polyp measuring 4 by 2.5 by 1.5 cm., and the smaller one, 2 cm. in each diameter. The plaque measured 1 cm. in each diameter.

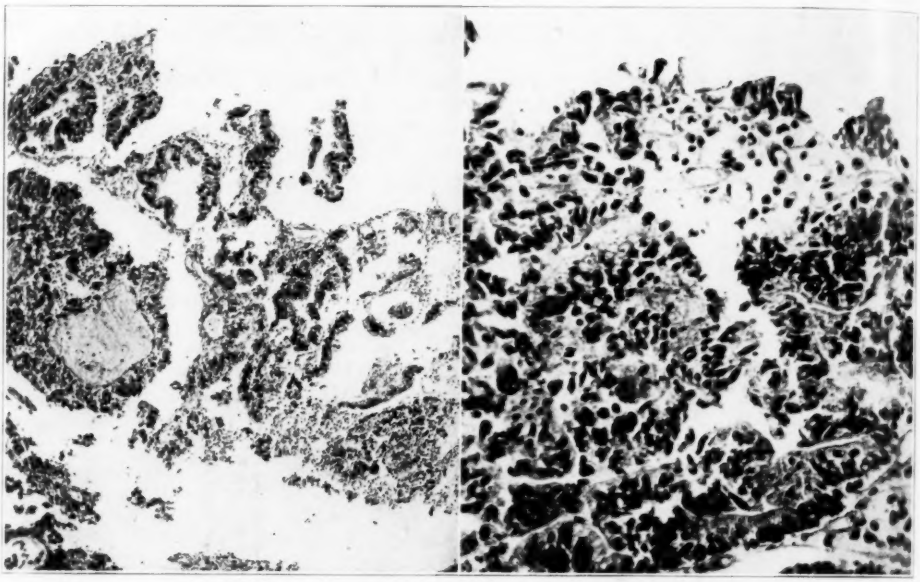

Fig. 17 (case 7).—Low and high power photomicrographs of larger polyp, showing malignant degeneration.

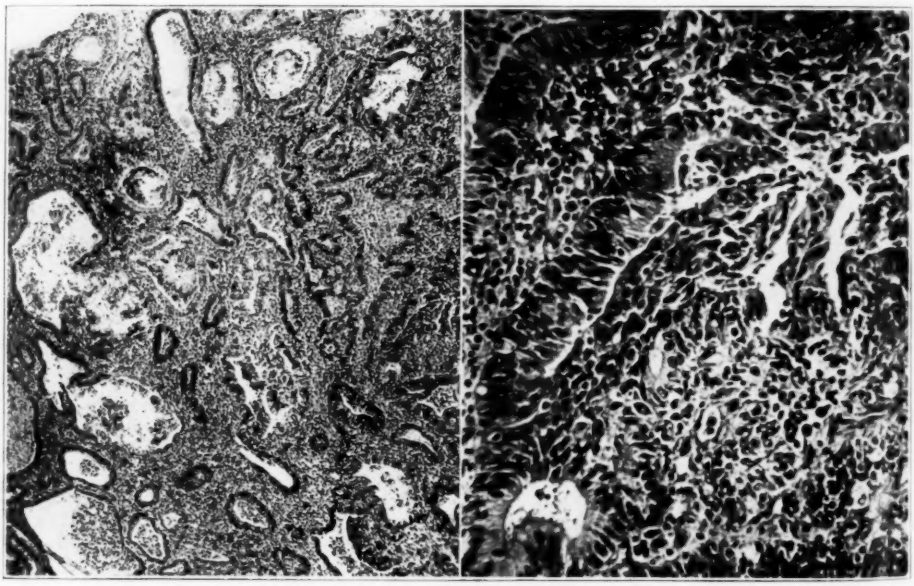

Fig. 18 (case 7).—Low and high power photomicrographs from smaller polyp, showing malignant degeneration.

The polyps, especially the larger one, were ulcerated, and both proved under microscopic study to be papillomatous and undergoing malignant degeneration (figs. 17 and 18).

CASE 8.—J. Q., a groceryman, aged 52, was admitted to one of our medical wards on Feb. 4, 1929, because of extensive edema of the legs and external genitalia. He had begun to have evidences of cardiac decompensation six months previously: palpitations, dyspnea, cough, cyanosis and edema. He had also been very pale, and a study of his blood before admission had showed the red blood cells reduced to

Fig. 19 (case 8).—Roentgenogram, viewed from in front, showing areas of vacuolization in the middle and lower thirds of the stomach. Roentgenologic diagnosis: polyposis of the stomach with possible malignant degeneration (1929).

1,110,000, the hemoglobin to 36 per cent and the white blood cells to 4,800. A diagnosis of primary pernicious anemia had been made, and he had been on a liver diet.

Examination revealed, in addition to the pallor and peripheral edema, orthopnea, fluid in the pleural cavities, an enlarged heart with impaired sounds, an enlarged liver, a pulsus alternans and considerable sclerosis of the peripheral blood vessels. The vibratory sense was diminished in each leg, but no other evidence of involvement of the cord was found.

At that time his blood showed: 3,100,000 red cells, 8,000 leukocytes and a hemoglobin percentage of 65. The platelets numbered 238,000. Four per cent of the red cells were reticulated. The urea nitrogen of the blood amounted to 14 mg. per hundred cubic centimeters. The van den Bergh test showed a delayed direct reaction and an indirect reading of 0.5 units. The Wassermann reaction was negative.

The patient improved with rest in bed and cardiac stimulation. Then, because of a tentative diagnosis of primary anemia and our routine practice in such cases, a fractional gastric analysis and a roentgenologic study of the digestive tract were undertaken.

The gastric analysis, with and without histamine, showed complete achlorhydria. On February 25, the roentgenologic study showed a marked gastric residue, a moderate continuous hyperperistalsis with motility less than commensurate and vacuolization in the middle third of the stomach (fig. 19). It was thought at first

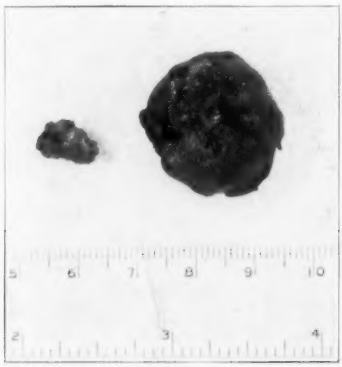

Fig. 20 (case 8).—Photograph of two specimens removed at operation.

that the vacuolization was due to food particles, but a repetition of the examination three days later, after twenty-hour hours on only liquid food, showed the same defects. A diagnosis of polyposis with possible malignant degeneration was then made.

In spite of the patient's circulatory condition and anemia, and especially because of his continued and constant loss of blood by the bowel, surgical intervention was determined on.

At operation under splanchnic anesthesia, one of us (E. L. E.) discovered a large polyp, which, when the stomach was opened, was seen to be about the size of a walnut and to be ulcerated. It was removed by severing its pedicle. Numerous smaller polyps were seen, but only one was removed.

The patient made a satisfactory surgical convalescence without complications and was discharged on April 2. On July 9, he reported to our followup clinic in excellent condition. He had regained his normal weight, had a good color and felt as well as ever. His heart was not enlarged. Blood counts were normal. No edema was present, and the abdomen showed only the incisional scar. A gastric specimen showed a persistence of the achlorhydria.

The specimen removed at operation (fig. 20) was ulcerated, and microscopic study showed it to be an adenocarcinoma (fig. 21).

The pertinent data on these eight cases of carcinomatous gastric polyp, which are outlined in table 1, may be summarized as follows:

1. All but one were males.

2. The majority (five of eight), at the time of recognition of the disease, was within the fifth decade of life, while one was 31 years of age, one was 52, and one was 61.

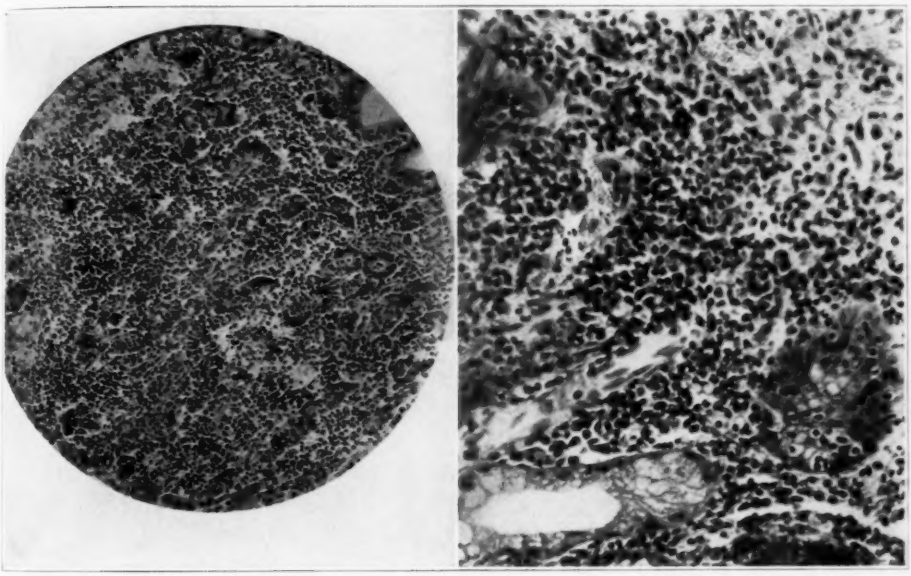

Fig. 21 (case 8).—Low and high power photomicrographs of larger polyp, showing adenocarcinomatous change.

3. The symptoms, in their order of frequency, were epigastric discomfort or pain, loss of weight, anorexia, vomiting that was sometimes bloody, nausea, pallor, the passage of blood by bowel, dizziness and diarrhea.

4. The physical signs were epigastric tenderness, the evidences of loss of weight and of anemia and Ewald glands (two cases).

5. Achlorhydria was present uniformly.

6. The Wassermann reaction was negative in every instance.

TABLE 1.—*Personal Group of Cases Showing Carcinomatous Change in Polyp of the Stomach*

Case	Year of Admission to Hospital	Sex; Age	Symptoms	Physical Observations	Observations on Gastric Analysis	Wassermann Reaction	Roentgenologic Observations				Diagnosis	Operative Observations; Operation Performed	Pathologic Observations	Comment
							Residue	Peristalsis	Motility	Defect				
1 F. A. D.	1919	M 31	Hemorrhage 18 months before; anorexia and pain in left upper quadrant for 2 months	Mass; visible peristalsis; Ewald gland	Achlorhydria	—	4	+	—	+	Gastric papilloma, possibly malignant	Polyp on greater curvature; metastasis Excision	Papilloma with malignant change	Diagnosed primary anemia 18 months before operation; died
2 E. K.	1923	M 45	Epigastric discomfort; later gnawing pain, relieved by food; hematemesis; lost 40 pounds; severe pain while under observation	Tenderness in epigastrium; enlarged liver	Achlorhydria	—	3	+	—	+	Duodenal ulcer or adhesions	Polyp on posterior gastric wall near pylorus Excision	At autopsy; carcinoma at cardia; papilloma, with malignant changes at pylorus	Original clinical diagnosis was peptic ulcer (before admission); died
3 G. L.	1924	M 45	Gnawing epigastric pain for 7 years; pain increased by activity; lost 20 pounds in last year	Negro; no abdominal observations	Achlorhydria	—	0	±	+	+	Papilloma or nodular carcinoma of pyloric region	Three polyps on posterior wall Excision	Papillomas with malignant change	Living after 5 years, and no evidence of recurrence
4 J. M.	1927	M 45	Nausea, vomiting, epigastric distress for 3 weeks; lost 15 pounds	Tenderness in gastric area	Achlorhydria; retention; blood	—	4	0	—	+	Probable carcinoma of pylorus, but syphilitic lesion possible	Polyp in duodenal bulb; infiltration of lower third of stomach Partial gastrectomy	Adenocarcinoma of polyp with intramural abscess; carcinoma of gastric wall	Died of secondary malignant lesions 18 months later

5 A. M.	1927	F 61	Diarrhea for 6 years; dizziness for 6 months; melena; colicky abdominal pain; lost 25 pounds	Tenderness in gastric and cecal areas	Achlorhydria; retention	—	3	+	+	+	Probable carcinoma of greater curvature of stomach	Three polyps on greater curvature Sleeve resection	One polyp malignant, one benign, one intermediate	Well after 18 months; gained 26 pounds
6 H. C.	1927	M 47	Anorexia for 2 years; pallor for 1 year; lost 22 pounds in a year	Pallor; mass in epigastrium; Ewald node	Achlorhydria	—	3	±	±	+	Large carcinoma or benign tumor on greater curvature	Polyp of posterior wall Partial gastrectomy	Ulcerated polyp with carcinomatous change	Diagnosed primary anemia originally; died a year later of gastric malignancy
7 W. C. H.	1928	M 44	Melena 6 months before; anorexia, bloody vomiting, nausea for 3 weeks; dizziness and weakness	Tenderness to left of umbilicus	Achlorhydria	—	2	—	—	+	Large polyp or carcinoma at pylorus	Two ulcerated polyps on posterior wall; indurated plaque, probably carcinomatous, higher on wall Partial gastrectomy	Papillomas with ulceration and malignant change	At work and apparently in good health 1 year later
8 J. Q.	1929	M 52	Anemia and symptoms of cardiac decompensation for 6 months	Pallor; signs of cardiac decompensation	Achlorhydria	—	3	+	—	+	Polyposis with possible malignant degeneration	One large and several small polyps Excision of large polyp	Adenocarcinoma of gastric polyp	Diagnosed primary anemia originally; good recovery

7. Roentgenologic study usually showed no interference with gastric peristalsis, a tendency to a decrease in gastric motility with retention of a part of the barium meal after six hours and invariably a vacuole defect in the stomach or duodenum.

8. A positive diagnosis of polyp with the suggestion that it might be malignant was made by the roentgenologists (Dr. H. K. Pancoast and Dr. E. P. Pendergrass) in two cases, and it was given as an alternate diagnosis with ordinary gastric carcinoma in three others; in two instances a probable carcinoma was suggested, and in one an ulcer or adhesions.

9. In all of the cases the polyp or polyps were demonstrated at operation.

10. One or more polyps in each case showed carcinomatous change, although polyps without such demonstrable degeneration were encountered.

11. At operation, excision of one or more polyps was done in four instances, a subtotal gastrectomy in three, and a sleeve resection in one.

12. Death occurred soon after operation in the first two cases, in both of which the disease was far advanced, and in two others it followed an extensive recurrence, in one twelve months, and in one eighteen months, after operation. Of the four patients living, one has a recurrence with hepatic metastasis, but the other three are well, a year, a year and a half and five years, respectively, after operation.

CASES FROM THE LITERATURE

Data of the same nature as those given in table 1 for our eight personal cases of malignant gastric polyps have been collected, as far as possible, on the twenty-four acceptable cases found in the literature. These data are assembled in table 2, and may be summarized as follows:

1. The male sex predominated, seventeen of twenty-one whose sex is known being men.

2. The age distribution was greater than in our personal series, ranging from 35 to 78 years. The great majority (81 per cent), as in our group, was 40 or more years of age.

3. The symptoms, in their order of frequency, were: abdominal pain, weakness, vomiting, anorexia, nausea, hematemesis, anemia and diarrhea.

4. The physical signs were chiefly those incident to anemia and epigastric soreness, although muscular rigidity, cachexia and a palpable mass were occasionally described.

5. Gastric analyses were recorded in only nine instances, and in eight of these achlorhydria was present. One of the eight cases (Struther's), which was studied two years and also nine months before malignancy was discovered, showed some free hydrochloric acid on those two occasions, but later there was an entire absence of such acid in the gastric contents. The only case showing any free hydrochloric acid (Meyer and Bram's case) had an associated ulcer near the pylorus, and malignancy was found only in the central portion of one of the many polyps (obviously an early case).

6. Wassermann reactions were reported in six instances, being clearly negative in all, although one patient had previously had a chancre and a positive reaction.

7 and 8. Roentgenologic study was made in thirteen cases, but the detailed observations were not reported in most instances. In all of these, however, defects in the gastric shadow were noted, and in five the diagnosis of a polyp or polyps was made; in the others, the ordinary type of carcinoma or an ulcer was suspected. These were the diagnoses made in our personal cases when the correct lesion was not appreciated.

9. The diagnosis of a polyp was made at operation in fifteen cases; in the remainder the lesion was discovered at necropsy. In three cases (one of Heinz, one of Brunn and Pearl and one of Chosrojeff) tumor tissue was recovered from the stomach by lavage, thus affording a diagnosis of malignancy.

10. As far as could be determined, ten of the patients presented malignant adenomas, while three were referred to as having malignant papillomas; the others were merely said to have malignant polyps. Sixteen had multiple polyps, and one (that of Lamas), like one of ours, had an abscess in a polyp.

11. The operations performed included five partial gastrectomies, eight excisions of one or more polyps and two gastrojejunostomies.

12. Of the fifteen patients operated on, we know only that two died promptly of surgical shock, three died later (in from three to twelve months) of a malignant process, one died after seven months of nephritis and one was living after eighteen months.

COMMENT

Pathogenesis.—The benign intragastric polyps are, in our experience, usually of an adenomatous construction, most of them being of the compoundly papillomatous type, and some of the smoothly papillomatous type. Certain authors, as Brunn and Pearl,[6] prefer to speak of them as adenopapillomatous. The early French writers, in referring to the cases of multiple polyp or of polyposis, preferred the term polyadenoma.

TABLE 2.—*Cases of Carcinomatous Gastric Polyp Collected from the Literature*

Author; Date of Report	Sex; Age	Clinical Notes	Free Hydrochloric Acid in Gastric Contents	Roentgenologic Observations	Pathologic Gastric Observations at Operation (o) or Autopsy (a)	Nature of Operation	Comment
Menetrier: Bull. Soc. anat. de Paris **2**: 736, 1886	M 35	No gastric symptoms.....	...	.....	Many polyps, some malignant and ulcerated; metastases to liver (a)	.....	Died of pneumonia; said to be first case of malignant gastric polyp reported
Menetrier: Arch. de physiol. norm. et path. **12**: 236, 1888	F 70	Epigastric pain for 5 years, diarrhea, blood in stools, cachexia	...	.....	Malignant adenomatous polyps with metastases (a)	.....	Referred to as "polyadénome polypeux," but description suggests malignancy
Bret: Arch. gén. de méd. **191**: 1345, 1903	M 60	Cardiorenal symptoms but no gastric symptoms	...	.....	Pedunculated tumor, size of orange, near pylorus with carcinomatous change in center (a)		
Menetrier and Chunet: Bull. et mém. Soc. de méd. d. hôp. de Paris **24**: 449, 1907	M 75	No digestive symptoms, only those of kidney disease; cardiac enlargement, edema, dyspnea	...	.....	Three small polyps and two larger sessile malignant tumors penetrating gastric wall (a)		
	F 73	Hemiplegic and nephritic symptoms	...	.....	A sessile tumor in pylorus with malignant change, the latter extending into wall; benign polyp on posterior wall (a)		
Verse: Arb. a. d. path. Inst. zu. Leipzig **4**: 1, 1908	M 78	Pain, anorexia, nausea, vomiting of blood, weakness	...	.....	Two soft malignant adenomatous polyps on greater curvature, one near pylorus (a)		
	F 42	.....	...	.....	A malignant adenomatous polyp near pylorus (a)		
Winternitz and Boggs: Bull. Johns Hopkins Hosp. **21**: 203, 1910	M 67	Negro; alcoholic; weakness and vomiting; arteriosclerotic and emaciated; ascites and many subcutaneous nodules	...	.....	Many benign and malignant polyps (a)	.....	Associated with cirrhosis of the liver, subcutaneous hemangioendotheliomas and intestinal lymphangio-endotheliomas; Wassermann reaction neg.

Chosrojeff: Beitr. z. path. Anat. u. z. allg. Path. **54**: 595, 1912	M 36	Bloody diarrhea for 2 years; epigastric pain, anorexia and weight loss; anemia; mass palpated	..	.....	Malignant polyps of adenomatous type with metastases (o)	Cautery excision of some polyps	Blood and tumor tissue in lavage water, which led to diagnosis of polypoid adenoma; good recovery from operation
Heinz: Cor-Bl. f. schweiz. Aerzte **42**: 354, 1912	M 35	.....	..	Pedunculated tumor	Three malignant adenomatous polyps (o)	Excision of 3 polyps	Tumor tissue in lavage water; developed severe anemia after operation
Chiarre: Deutsche med. Wchnschr. **39**: 2349, 1913	F 44	.....	..	.....	Malignant adenomatous polyps at pylorus (a)	.....	Pylorus intussuscepted into duodenum
Finney and Friedenwald: Am. J. M. Sc. **154**: 633, 1917	..	.....	..	.....	Papillomatous polyps throughout stomach with malignant change in some near pylorus	.....	Museum specimen, College of Physicians, Baltimore
	M 50	Pain, nausea, vomiting, weakness, loss of weight for 9 months; poorly nourished, large liver, epigastric mass; melena	0	Carcinoma of stomach	Malignant papillomatous polyp near pylorus and scirrhous carcinoma of stomach wall; metastasis to glands (o)	Resection and posterior gastrojejunostomy	Immediate result satisfactory
	M 55	Weakness and loss of weight for 3 months; anemia and melena	0	Carcinoma of stomach	Single adenopapilloma with broad base (sessile) with ulceration and malignant change (o)	Cautery excision	Died of carcinoma of stomach a year later; Wassermann reaction negative
Gassman: Arch. f. Verdauungskr. **28**: 236, 1921	M 57	Indigestion for years; pain, anorexia, loss of weight for 2 months	0	Polypoid tumor	Malignant adenomatous polyp, size of apple, on lesser curvature (o)	Excision	Immediate result satisfactory; gained 5 pounds in 5 months
Zabel, quoted by Bryan: Southwest Med. **6**: 225, 1922	..	.....	..	.....	Malignant papilloma (a)	.....	Megastoma intestinale in tumor mass
Struthers: Surg. Gynec. Obst. **38**: 610, 1924	M 48	Pain in epigastrium and back for a year; weakness, constipation, anemia	20	Lesion at pylorus	Hypertrophied pyloric mucosa producing obstruction (o)	Gastrojejunostomy	First admission to hospital; Wassermann reaction negative
		Pain increased; vomiting....	20	Gastrojejunal ulcer	Gastric polyposis obstructing both outlets from stomach (o)	Partial gastrectomy	Second admission 15 months later
		Pain, nausea, vomiting, weakness, anemia	0	Carcinoma of stomach	Carcinoma with metastases to ribs	.....	Third admission 9 months later; died 3 months later
Meyer and Brams: Surg. Gynec. Obst. **41**: 311, 1925	M 53	Periodic attacks of pain relieved by vomiting for 2 years; anorexia, nausea, weight loss, tenderness in left upper quadrant	15	Defect on lesser curvature near pylorus; probably carcinoma	Typical peptic ulcer near pylorus and many polyps nearby; polyps not ulcerated but one showed malignancy in center (o)	Resection	Earliness of case and ulcer probably explain acidity; (only case showing any free hydrochloric acid); Wassermann reaction negative

TABLE 2.—*Cases of Carcinomatous Gastric Polyp Collected from the Literature—Continued*

Author; Date of Report	Sex; Age	Clinical Notes	Free Hydrochloric Acid in Gastric Contents	Roentgenologic Observations	Pathologic Gastric Observations at Operation (o) or Autopsy (a)	Nature of Operation	Comment
Brunn and Pearl: Surg. Gynec. Obst. **43**: 354, 1926	M 53	Pain, anorexia, nausea, weakness; epigastric tenderness, anemia (hemoglobin 55 per cent)	0	Filling defects on greater curvature, diagnosed polyps	Mass of polyps, size of orange, on greater curvature, with metastases to glands (o)	Excision	Died of shock from operation; achylia 25 years before; 9 months before this operation had resection for ulcer which was benign; chancre at 32 years; Wassermann reaction positive; then after treatment, negative
Brunn and Pearl: ibid.	M 58	Weakness, dyspnea, edema, loss of weight; cachexia and anemia (hemoglobin 40 per cent)	0	Filling defects along greater curvature, one near cardia; diagnosed polyps	Malignant adenopapillomatous polyps on posterior wall near greater curvature, showing ulceration (o)	Cautery excisions of large polyps	Malignant tissue recovered from lavage led to diagnosis of probable malignant polyps; well for 17 months, then mass felt; Wassermann reaction negative
Brunn and Pearl: ibid.	M 45	Pain for 18 months, anorexia, eructations, weakness, dizziness, vomiting, weight loss; alcoholic; cachexia and anemia (hemoglobin 52 per cent)	0	Filling defects, diagnosed multiple polyposis	Fourteen adenopapillomatous polyps with malignant change; wall of stomach and glands involved one polyp ulcerated (o)	Partial gastrectomy	Died of shock from operation
Balfour and Henderson: Ann. Surg. **85**: 354, 1927	..	Anemia.....	0	.....	Malignant polyp in upper third of stomach (o)	Cautery excision	Inoperable carcinoma of stomach 4 months later
Lamas: Arch. d. mal. de l'app. digestif **18**: 261, 1928	M 50	Pain, vomiting of blood; epigastric tenderness	..	Niche on lesser curvature, diagnosed ulcer	Diffuse polyposis with malignant change in one of large polyps; abscess in polyp (o)	Excision	Immediate result satisfactory
Horsley: Ann. Surg. **88**: 554, 1928	M 77	Indigestion for 2 years; nausea, vomiting and weight loss; emaciation	..	Pyloric obstruction	Malignant polyp at pylorus; malignant ulcer associated (o)	Partial gastrectomy	Died 7 months later from nephritis

and Menetrier [14] divided them into the diffuse form (polyadénome polypeux) and the localized form (polyadénome en nappe). Although adenoma is the term most commonly used, a capsule is not usually found. This led Mills [5] to look on them as papillomas rather than adenomas. He expressed the belief that they begin as simple thickenings of the mucous membrane, later becoming sessile growths and finally true polyps. It is probable that they begin in much the same way that nasal polyps do, being at first merely low elevations of the mucosa and later becoming pedunculated. Ewing [15] regarded these nasal polyps as pseudoneoplasms of inflammatory origin, although they may eventually assume various pathologic forms: fibromas, adenofibromas or myxomas. It would seem that the young gastric polyps might be regarded similarly as pseudoneoplasms, eventually taking on an adenomatous form and sometimes showing malignant degeneration.

This comparison with nasal polyps suggests that the gastric polyps have an inflammatory origin. Menetrier,[16] who in 1886 reported the first case with malignant change, believed in such an origin, and called particular attention to their occurrence in patients with arteriosclerosis. Bret [17] also noted this association in reporting a case with circulatory, but not gastric, symptoms. Although their reasoning is not convincing today, other arguments for an underlying inflammatory lesion may be presented. Chief among these is the fact that achlorhydria is so frequently associated, not only in the malignant cases, but also in those that are still benign. Strauss, Meyer and Bloom [18] stated that in cases of polyposis, achylia is a constant observation. One of Brunn and Pearl's [6] patients had achlorhydria twenty-five years before malignancy was discovered. Faber [19] pointed out that achlorhydria results from chronic gastritis even when ordinary microscopic study shows no evidence of such a lesion. Furthermore, it is well known that polyps on other mucous membranes develop as a result of inflammatory changes: nasal polyps in cases of chronic rhinitis and colonic polyps in cases of chronic colitis.

14. Menetrier, P.: Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac, Arch. de physiol. norm. et path. **1-2**:236, 1888.

15. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

16. Menetrier, P.: Polyadénomes gastriques et cancer de l'estomac, Bull. Soc. anat. de Paris **2**:735, 1886.

17. Bret, J.: Du polyadénome polypeux et de l'adénopapillome de l'estomac, Arch. gén. de méd. **191**:1345, 1903.

18. Strauss, A. A.; Meyer, J., and Bloom, A.: Gastric Polyposis, Am. J. M. Sc. **176**:681 (Nov.) 1928.

19. Faber, K.: The Etiology and Pathogenesis of Achylia Gastrica, Am. J. M. Sc. **172**:1 (July) 1926.

Also, the frequent occurrence of benign polyps in the stomach, the seat of ulcer or carcinoma, suggests an inflammatory origin for the polyps. Chronic gastritis is commonly associated with these two diseases of the stomach. Douglas,[20] Mills [5] and Stewart [21] each reported a case of gastric carcinoma with associated benign polyps. Both Douglas and Stewart believed that the carcinoma might have originated in a similar benign polyp, but Mills expressed the opinion that this had not occurred in his case because of the distance of the malignant lesion from the benign ones and its fundamentally different structure. However this may have been, one may assume that a chronic gastritis was present. In Meyer and Brams' [22] case of gastric polyps, one of which was carcinomatous, there was an ulcer near the polyps, and other such cases have been reported. Here again one can easily conceive of a localized inflammation about the ulcer as a basis for the polyp formation.

Other etiologic factors, such as hereditary influences, congenital malformations, systemic lymphatic hypertrophy, metabolic disturbances, alcoholism, sclerosis of gastric vessels and such specific chronic infections as syphilis and tuberculosis, have been suggested; there is not sufficient evidence, however, to justify further consideration of these possible factors at this time.

The development of malignancy in benign gastric polyp is favored by trauma incident to gastric peristalsis and to the passage of coarse articles of food and also by the adenomatous nature of the benign lesion. Ewing [15] suggested that all the bulky polypoid carcinomas of the stomach may have their origin in such benign polyps.

The possibility of a carcinomatous polyp springing directly from a primary malignant process in the gastric wall cannot, of course, be denied. Our case 6, presenting a polypoid medullary carcinoma with a thick firm stalk, may be an instance of such development. In all the other cases, however, no gross evidence of malignant involvement of the pedicle or of the wall of the stomach itself was present, and gastric peristalsis, as indicated by fluoroscopic study, was not interfered with. That the lesions in most instances had assumed the form of polyps before malignancy developed is suggested also by their frequent association with other polyps still benign, by the observation, in some of them, of malignant change in only a small area of an affected polyp and by the long duration of some of the polyps before the evidences of serious illness were manifest.

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20. Douglas, J.: Benign Tumors of the Stomach, Ann. Surg. **77**:580 (May) 1923.

21. Stewart, M. J.: Carcinoma of the Stomach in Association with Multiple Polypoid Adenomata, J. Path. & Bact. **18**:127, 1913.

22. Meyer, K. A., and Brams, W. A.: Non-Carcinomatous Tumors of the Stomach, Surg. Gynec. Obst. **41**:311 (Sept.) 1925.

Sex and Age Incidence.—Consideration of the data presented on these two groups of cases seems to determine, without further comment, that the great majority of the malignant cases occur in the male sex (80 per cent), and that the age incidence is the same as that for the more ordinary variety of gastric carcinoma (83 per cent of our thirty-two patients being over 40 years of age).

Symptomatology.—Uncomplicated benign gastric polyp gives rise to no symptoms, and those presented by these two groups of malignant cases can be explained most satisfactorily on the basis of the three complications originally referred to:

1. The mere presence of a malignant gastric lesion, no matter what its location or conformation, is well known to lead to anorexia, nausea and loss of weight and eventually to emaciation. These phenomena were encountered frequently in our cases and in those reported in the literature.

2. Pyloric obstruction accounts for the pain and the vomiting and incidentally is a factor in the production of anorexia and nausea. It will be noted that these disturbances are often intermittent. This periodicity can be explained by the fact that the polyps, frequently having pedicle attachments in the antral region, are movable in and out of the narrow pyloric canal, thus producing intermittent obstruction. Sometimes they slip through into the duodenal bulb (figs. 1, 3, 7 and 15). In one of our cases (case 4) the polyp was found at operation in the duodenal bulb and could easily be pushed back and forth through the sphincter. The same procedure was carried out at operation in case 7, though the polyp in that instance was originally palpated on the gastric side. In case 3 (fig. 2) the mass could be identified by roentgenologic study in the pyloric antrum.

Pain was present in 70 per cent of the entire series. It was usually referred to as gnawing, crawling or burning; sometimes it was colicky and associated with vomiting. No definite relationship to the intake of food could be determined, although in one instance at least it came on regularly about two hours after eating, thus suggesting a diagnosis of ulcer. Two patients had a sensation of something alive in the stomach, and in both of these the distress was greatest at night, especially when lying on the right side. Relief was obtained by vomiting and by rolling onto the left side. In many cases intervals of complete freedom from distress, lasting days or weeks, were experienced.

3. Hemorrhage is a common occurrence, not only in malignant polyps of the stomach, but also in the benign ones. It may be minute and persistent, as probably in our cases 1 and 8, or profuse with hema-

temesis, as in our case 7. It accounts chiefly for the symptoms of weakness and dizziness and for the vomiting of blood and the melena.

Such hemorrhage from gastric polyps deserves special consideration, since in certain cases it may be the only lead in arriving at a diagnosis. Furthermore, if a bleeding gastric polyp is not considered in every case of obscure anemia, certain cases will be entirely misdiagnosed. This is strikingly illustrated by the fact that three of our eight cases had been diagnosed originally as primary anemia (cases 1, 6 and 8) by competent internists, one of them eighteen months before a gastric tumor was suspected. In case 7 of our personal series the patient had melena six months before the proper diagnosis was made by roentgenologic study, and even after a profuse hematemesis was allowed to return to work without adequate investigation. Thus it will be seen how these three complications—malignancy, pyloric obstruction and hemorrhage—account for the chief symptoms complained of.

Diarrhea alone is not explained. In our case 5, the patient had this as an initial complaint, and it had been present for six years. She had, in addition to gastric polyps, at least one polyp in the sigmoid, but this could not have caused the diarrhea, which ceased after operation on the stomach. Achlorhydria also may be thought of as an explanation, but again the disappearance of the diarrhea after operation precludes such a possibility. It occurred in two of the cases collected from the literature.

Diagnosis.—In spite of the explanation of the symptoms given, it cannot be claimed that they are sufficiently specific, even when all are present, to lead to a diagnosis. In one of our cases, however, on the basis of the symptoms alone and objective evidence of anemia, such a diagnosis was ventured, and in another case, not reported because the patient has not as yet come to operation, the diagnosis was suggested and subsequent roentgenologic study seemed confirmatory. At least it may be remarked that a middle-aged man suffering irregularly from epigastric distress, anorexia, nausea and vomiting, with blood in the vomitus and feces, achlorhydria and some anemia, should be suspected not only of having carcinoma of the stomach, but of having the special variety under discussion. In this group of data the irregular occurrence of the obstructive phenomena is most suggestive.

The observations of achlorhydria and of blood in the gastric contents lend support to the diagnosis, but do not, of course, differentiate from ordinary mural carcinoma.

The roentgenologic study is the most important means of making the specific diagnosis of a gastric polyp, but does not indicate its malignancy. It was successful in five of our eight cases. The important roentgenologic observations are a characteristic defect and decreased

motility. Peristaltic waves are not usually interfered with because of the superficial attachment of the polyp to the wall of the stomach. Their frequency and depth are usually increased (hyperperistalsis). The defect appears as a vacuole, smooth in outline and usually situated in the pylorus or duodenum. Several such defects may appear. The presence of one such defect in the duodenal bulb may be associated with others in the stomach. It is conceivable that a duodenal vacuole may be found at one examination and not at another, although we have not had this experience. The motility also, doubtless, varies from time to time depending on the position of the polyp.

When a polyp is so demonstrated by roentgenologic study, and the symptomatology and observations of gastric analysis suggest malignancy, a diagnosis of carcinomatous polyp is justified.

Surgical Features.—When the polyp is small, or the pedicle long, extreme difficulty may be encountered in its discovery even by direct palpation of the viscera at operation. In the first patient operated on by one of us (E. L. E.) the accidental finding of an indefinite soft mass in the pyloric region which suddenly, during digital examination, slipped away and then later was found in the duodenum, from which, on palpation, it again promptly slipped back into the stomach, suggested the lesion. Because of this experience, when extragastric manipulation failed to reveal the mass in another case, in which polyp had been diagnosed by roentgen study, a gastrotomy was performed. When the stomach was opened, the lesion was readily made to protrude through the wound (case 3, illustrated in the original report).

Gastrotomy may thus establish the diagnosis in cases that would otherwise be overlooked even at operation. The fact that such polyps at their point of origin are usually attached only to the inner coats of the gastric wall accounts for the occasional difficulty of finding them without direct inspection of the interior of the stomach. A direct gastroscope is an aid in such investigation. Failure to open the stomach doubtless accounts for some of the negative operative observations in cases of suspected ulcer which are really cases of gastric polyp. Such patients would continue to have symptoms even if the usual gastrojejunostomy, as the surgical treatment for ulcer, was performed. Certainly when the clinical data suggest a polyp the stomach should be opened and explored.

The surgical procedures in cases of polyp must be suited to the condition found at operation. In view of the high incidence of malignancy in cases of polyp, the more extensive subtotal gastrectomy with removal of the lymph nodes is the wisest procedure. The former methods of local excision, cautery removal, ligation and removal and sleeve resection should give way to the more radical methods. The fact that

malignancy cannot be determined macroscopically, nor often by the microscope except after numerous sections are made, is reason enough for radical treatment for every gastric polyp.

CONCLUSIONS

On the basis of the data set forth in this paper regarding eight personal cases of carcinomatous polyp of the stomach and regarding twenty-four cases previously reported in the literature, a total of thirty-two cases, we feel justified in presenting the following conclusions:

1. Carcinomatous polyp of the stomach is more frequent than has been generally believed, having been found in 35 per cent of all the cases of intragastric polyp that we have studied adequately (eight of twenty-three), and both the history and the pathologic data suggest that it usually originates in polyp of a benign nature.

2. The benign intragastric polyps that show this tendency to malignant change are usually of an adenomatous construction.

3. Most of the patients showing such malignant change are males (83 per cent), and the age incidence is the same as for mural gastric cancer.

4. The symptoms are those of any malignant gastric lesion with, in addition, those of the two other common consequences of gastric polyp —intermittent pyloric obstruction and hemorrhage.

5. The hemorrhage may be frank or occult; it not infrequently leads to an erroneous diagnosis of primary anemia (three of our eight personal cases). Consequently, gastric polyp should be considered in all cases of unexplained anemia.

6. Roentgenologic study alone often makes the diagnosis of gastric polyp, and malignancy may be suspected on the basis of the clinical picture.

7. Gastric polyp may be overlooked at operation, and special procedures, including gastrotomy and exploration of the interior of the stomach with a gastroscope, are indicated when any clinical suspicion of a polyp exists or when a suspected ulcer is not found.

8. All gastric polyps, when demonstrated, deserve the radical surgical treatment commonly employed in cases of known or suspected gastric carcinoma.

LOW BASAL METABOLISM WITHOUT MYXEDEMA *

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In a study of low basal metabolism following thyrotoxicosis, Thompson and Thompson [1] were impressed by its frequency and by the fact that an underfunction of the thyroid could be demonstrated in only a comparatively small number of cases. Several of the patients appeared to be healthy in spite of low metabolism. These results made it appear desirable to make a study of low basal metabolism in general.

A low metabolic rate following toxic goiter has been observed by Elliott,[2] Jordan [3] and Cabot [4] in a few patients who did not appear myxedematous. Means and Burgess,[5] in reviewing the basal metabolisms of the first 1,000 subjects on whom such a determination was made at the Massachusetts General Hospital, reported rates of minus 15 per cent or lower in 16 cases exclusive of disorders of the thyroid. Boothby and Sandiford,[6] in summarizing the metabolism data of 8,614 subjects

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1. Thompson, W. O., and Thompson, P. K.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type Without Myxedema, with Special Reference to the Rôle of Iodine Therapy, J. Clin. Investigation **5**:441, 1928; Low Basal Metabolism Following Thyrotoxicosis: II. Permanent Type Without Myxedema, ibid. **5**: 471, 1928; Temporary and Permanent Myxedema Following Treated and Untreated Thyrotoxicosis, ibid. **6**:347, 1928; Significance of Low Basal Metabolism Following Thyrotoxicosis, Am. J. Surg. **7**:48, 1929.

2. Elliott, C. A.: Results of Thyroidectomy for Hyperthyroidism as Indicated by Examination a Year or More Following Operation, Tr. A. Am. Phys. **41**:93, 1926.

3. Jordan, S. M.: Basal Metabolic Rates and Their Relation to End-Results in Thyroid Disease: A Statistical Study, Arch. Surg. **11**:1 (July) 1925.

4. Cabot, R. C.: Case 12182, Boston M. & S. J. **194**:844, 1926.

5. Means, J. H., and Burgess, H. W.: The Basal Metabolism in Nontoxic Goiter and in Borderline Thyroid Cases, Arch. Int. Med. **30**:507 (Oct.) 1922.

6. Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism Data on 8,614 Subjects With Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, J. Biol. Chem. **54**:783, 1922.

at the Mayo Clinic, found a basal metabolism below minus 15 per cent in 103 patients who had no disease of the thyroid.

A few persons who seemed to be healthy in spite of basal metabolisms of minus 19 to minus 25 per cent have been reported by Sturgis,[7] Wishart,[8] Strouse and Binswanger[9] and King[10] among men in the temperate zone, and by Sison and Ignacio[11] among Filipinos. In ten men (physicians, lawyers, engineers) between 23 and 40 years of age who had no apparent disease and who had lived all their lives in or near Rio de Janiero, De Almeida[12] found an average heat production 24 per cent lower than the average value of the Aub-Du Bois standard normal of 39.7 calories per square meter of body surface per hour. From these data he concluded that the metabolism of white men is lower in the tropics than in temperate climates.

It has been shown by Ohler and Ullian[13] (37 cases), Higgins[14] (43 cases), Lawrence[15] (42 cases), and more recently by Koehler[16] (288 cases), that a basal metabolism from 10 to 25 per cent below the standard normal, without myxedema, is not an infrequent observation. Most of these authors do, however, credit some degree of thyroid insufficiency for these low rates, and classify their cases as hypothyroidism, incipient hypothyroidism and thyroid failure without myxedema. Some of their patients apparently showed clinical improvement coincident with a rise

7. Sturgis, C. C.: A Clinical Study of Myxedema With Observations of the Basal Metabolism, M. Clin. North America **5**:1251, 1922.

8. Wishart, G. M.: The Variability of Basal Metabolism, Quart. J. Med. **20**: 193, 1927.

9. Strouse, S., and Binswanger, H. F.: The Symptom Complex Resembling Hyperthyroidism Without Increased Metabolism, J. A. M. A. **88**:161 (Jan. 15) 1927.

10. King, J. T., Jr.: Observations on the Menopause: I. The Basal Metabolism After the Artificial Menopause, Bull. Johns Hopkins Hosp. **39**:281, 1926.

11. Sison, A. B. M., and Ignacio, M.: Basal Metabolism Among Filipinos, J. Philippine Islands M. A. **7**:416, 1927.

12. De Almeida, A. O.: Le métabolisme minimum et le métabolisme basal de l'homme tropical de race blanche, J. de physiol. et de path. Gén. **18**:713, 1919.

13. Ohler, W. R., and Ullian, L. J.: Clinical Survey of 1000 Cases on Whom Basal Metabolism Studies Have Been Made, M. Clin. North America **8**:1495, 1925.

14. Higgins, W. H.: Management of the Hypothyroid, South. M. J. **20**:779, 1927; Incipient Hypothyroidism: A Clinical Study, J. A. M. A. **85**:1015 (Sept. 26) 1925.

15. Lawrence, C. H: The Physiological Background for the Symptoms of Thyroid Failure, with a Consideration of the Results of Treatment, Boston M. & S. J. **196**:43, 1927; Thyroid Failure Without Myxedema, M. Clin. North America **8**:1779, 1925.

16. Koehler, A. E.: Differential Diagnosis Between Hypothyroidism and Hyposuprarenalism, J. A. M. A. **91**:1457 (Nov. 10) 1928.

in metabolism during the administration of desiccated thyroid. Koehler was unable to classify many of his patients and considered some to have an underfunction of the suprarenal cortex, although the evidence on which this diagnosis is based is inconclusive.

The foregoing reports indicate that low basal metabolism without myxedema is a common observation, and that the types of patients falling within this classification are thought to be: (1) those who are apparently healthy and normally have a low metabolism; (2) those with hypothyroidism too mild to result in myxedema, and (3) those in whom a low metabolism is associated with pathologic conditions other than underfunction of the thyroid.

TABLE 1.—*Comparison of the Basal Metabolism in One Hundred and Ninety-Six Cases with Low Rates without Myxedema and in Eighty Cases of Typical Myxedema* * †*

Basal Metabolic Rate, Per Cent Normal	Without Myxedema		With Typical Myxedema	
	Number of Cases	Per Cent of Cases	Number of Cases	Per Cent of Cases
Minus 11 to −15	27	14	3	4
−16 to −20	111	57	10	12
−21 to −25	50	25	18	23
Below −25	8	4	49	61
Total	196	100	80	100

* Aub-Du Bois standards were used in the calculations.

† The thirteen patients who apparently had hypothyroidism without myxedema are included among those without myxedema.

DATA

Of 6,655 patients of all types, 1,255 (19 per cent) had one or more metabolic rates below minus 10 per cent. Eliminating those cases in which the thyroid function seemed definitely subnormal (130 cases of myxedema and 16 cretins), those in which the diagnosis of myxedema was doubtful (26 cases), those in which data had been previously reported [17] (50 cases), and those in which data were unsatisfactory,[18] there remains a group of 196 cases which forms the basis of this paper.

These patients did not appear to be myxedematous, and most of them appeared to receive no clinical benefit from the administration of

17. Thompson, W. O., and Thompson P. K. (footnote 1, first, second and fourth references).

18. In this group are included 236 private patients of physicians outside the clinic, who were omitted because of varying criteria of diagnosis and our inability to secure complete data; and 538 patients who had either only one low basal metabolic rate among several normal ones, or a single determination which was low.

enough desiccated thyroid [19] to raise the metabolic rate to the normal level. It was thus inferred that in the majority there was no definite evidence of subnormal thyroid function.

In table 1, these 196 cases and 80 cases of myxedema [20] for which data were sufficient, are divided for comparison into groups on the basis of the metabolism tests alone. The low metabolism in each case has been averaged before being placed in its division. It is of interest that the basal metabolic rate was below minus 20 per cent in 84 per cent of the patients with myxedema, but in only 29 per cent of the patients without myxedema. Whereas in only 8 (4 per cent) of 196 patients without myxedema there was a basal metabolism below minus 25 per cent, in the 80 patients with myxedema there were 49 (61 per cent) with a basal metabolism below 25 per cent.

CLASSIFICATION

These 196 patients may be tentatively grouped as follows: [21]

I. Those who appeared to be normal (11 patients).

II. Those who appeared to be abnormal (185 patients).

A. Those who were nervous, worried, easily fatigued, and sensitive to cold, who often had diminished catamenia, and probably suffered from some endocrine disturbance (79 patients).

B. Those in whom the outstanding abnormality appeared to be irregularity of menstruation (always scantiness or temporary amenorrhea or both) (21 patients).

C. Those who probably had mild hypothyroidism, but who had no detectable edema (13 patients).

D. Those with various conditions not included in the preceding groups that are sometimes associated with low basal metabolism, e. g., starvation, pituitary tumor, muscular atrophy, etc. (72 patients).

I. *Normal Persons.*—There were 11 patients who, so far as we were clinically able to determine, were normal except for a basal metabolism lower than the accepted standard (minus 11 to minus 24 per cent). The following case history is presented as typical:

Mrs. M. H. (lab. no. 5745), a laboratory technician, aged 25, complained merely of sensitiveness to cold weather. There were no abnormal clinical observations, except a basal metabolic rate of minus 24 per cent. Two grains (0.13 Gm.)

19. Armour's desiccated thyroid was used in all cases.

20. These 80 cases of myxedema form an unselected group in which more than one basal metabolism determination was made before thyroid was administered. The data on the other cases of myxedema are less complete.

21. The classification given here is based largely on the symptoms presented by the patients and, for the most part, makes no attempt to differentiate clinical entities.

of desiccated thyroid daily caused the rate to rise to plus 5 per cent, but also caused palpitation, marked ease of fatigue and an elevation of pulse rate from 68 to 120. When thyroid was omitted these symptoms disappeared, the metabolism returned to minus 24 per cent, and the patient felt well again.

II. *Abnormal Persons.*—Of the 185 subjects who were abnormal, 36 were males and 149 were females. Their ages ranged from 10 to 70 years, with fairly even distribution for each decade from the second through the fifth, only six cases falling outside these limits. Although the symptoms, physical signs and basal metabolism were repeatedly observed, it was only in an occasional instance that any material improvement was noted following the administration of desiccated thyroid. None of these cases was typical of myxedema clinically, although they often showed a few symptoms that are also characteristic of that disorder, such as ease of fatigue.

A. Nervous, Worrying Persons Who Become Fatigued Easily: These patients, only 6 of whom were males, formed the largest group of the series. They presented the following clinical picture: The symptoms (listed in order of frequency) were lack of endurance, marked nervousness, marked tendency to worry and emotional upsets on slight provocation, sensitiveness to cold, numbness and tingling of extremities, constipation, headache, vague pains, dizziness, palpitation and often dyspnea on exertion.

The signs were as follows: The basal metabolic rate was below normal in all cases. Weight was normal in 49 per cent, less than average in 31 per cent, and more than average in 20 per cent of the cases. The systolic blood pressure was from 104 to 198 mm. of mercury and the diastolic pressure from 60 to 100 mm. of mercury. The pulse rate was below 76 beats per minute in 59 per cent and 76 beats per minute or above in 41 per cent. Catamenia was normal in 40 per cent of women and irregular (delayed and scanty) in 60 per cent of women. There were no changes in the hair, skin or nails.

In addition to showing a few symptoms also shown by patients with myxedema (notably ease of fatigue, and in some cases sensitiveness to cold and diminished catamenia), the clinical picture presented by these patients was similar in some respects to that in other conditions unassociated with a low metabolism. For example, marked nervousness on slight provocation, marked tachycardia on excitement and moderate exertion and lack of endurance are said to be outstanding symptoms in the patients with "mild hyperthyroidism" and slightly increased metabolism reported by Miller and Raulston.[22] Dizziness, insomnia, fatigue, palpi-

22. Miller, J. L., and Raulston, B. O.: The Recognition of Mild Hyperthyroidism, J. A. M. A. **79**:1509 (Oct. 28) 1922.

tation, excitability, irritability, headaches, indefinite gastro-intestinal irregularities, loss of weight and occasionally increased blood pressure were the most prominent symptoms in the group of patients described by Strouse and Binswanger [9] as having a symptom-complex resembling hyperthyroidism without increased metabolism. Many of these symptoms were also present in the patients with "autonomic imbalance" but normal metabolism described by Kessel and Hyman,[23] and are also complained of by patients with "effort syndrome."

Thus it is at present impossible to be sure that the various clinical abnormalities and the reduction in basal metabolism in patients in group A are the results of the same pathologic condition. Many of the patients were referred to us with a diagnosis of neurasthenia. However, just because we do not at present know the diagnostic significance of the signs and symptoms these patients presented, is not a good reason for labeling them as neurasthenic types. It has previously been emphasized that these patients do not show a favorable clinical response to therapeutic doses of desiccated thyroid. Their metabolism may be raised to standard normal, but there is either no change in their condition or they may develop thyroid intoxication, i. e., palpitation, rapid pulse, increased nervousness and possibly precordial pain. The response to thyroid is, in our opinion, the single most important criterion in determining the presence or absence of underfunction of the thyroid.

The following case history is typical of the group:

Mrs. A. T. (figs. 1 and 2), an American housewife, aged 43, first came to the metabolism laboratory on March 27, 1928, complaining of headaches, ease of fatigue, sensitiveness to cold weather, coldness and numbness of the extremities, nervousness, insomnia and worry, all of which had been present as long as the patient could remember. At times the headaches were accompanied by nausea and vomiting. She had never been pregnant. The results of the physical examination were essentially negative. She was well developed and well nourished. The skin was soft, warm and moist, the hair of normal texture and distribution. The thyroid gland was barely palpable and of normal consistency. Examination of the chest, heart, abdomen, pelvis and rectum showed no abnormalities. There were no signs of myxedema. The systolic blood pressure was 140 mm. of mercury and diastolic pressure 80 mm. During the course of her visits to the clinic, laboratory studies revealed no abnormalities in the urine, a hemoglobin concentration of 80 per cent, a red blood cell count of 5,000,000 per cubic millimeter and a white blood cell count of 7,250 per cubic millimeter. Gastric analysis, roentgenograms of the sella turcica and of the gastro-intestinal tract, and food tests in the anaphylaxis clinic gave normal results. Special examinations of the eyes and ears showed nothing remarkable. The initial basal metabolic rate was minus

23. Kessel, L., and Hyman, H. T.: Studies of Graves' Syndrome and the Involuntary Nervous System: II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), Am. J. M. Sc. **165:** 513, 1923.

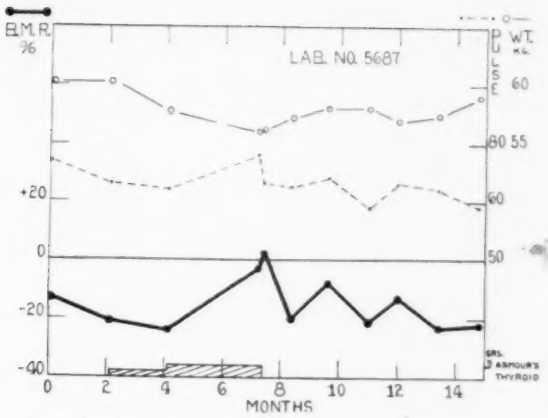

Fig. 1.—Chart showing low basal metabolism in a nervous worrying type of woman, aged 43, who had had severe headaches frequently since childhood and tired very easily. Three grains of desiccated thyroid daily produced no clinical improvement although the metabolism was raised to normal. (In this and subsequent figures, the cross-hatched areas denote periods of treatment with desiccated thyroid.)

Fig. 2.—Comparison of photograph of Mrs. A. T. on the left (taken Dec. 11, 1928, when the basal metabolic rate was minus 20 per cent) with that of a typical patient with myxedema (Mrs. M. V. L.) on the right of about the same age and with about the same depression of the basal metabolic rate.

13 per cent, and a second test was minus 21 per cent. Three grains (0.19 Gm.) of desiccated thyroid daily raised it to plus 2 per cent, without clinical improvement; that is to say, she continued to be easily fatigued, to have headaches and to be sensitive to cold.

A few of the other patients of this type to whom desiccated thyroid was administered felt a little better at times while taking it, but the improvement was short-lived. In most instances there was no change in symptoms.

B. Patients Whose Chief Complaint Was Diminished Menstruation: There were 21 patients who complained chiefly of diminished menstruation.[24] In the majority of instances it was delayed from two weeks to three months, and a few patients were observed who had amenorrhea for a year or more. Since amenorrhea may be associated with several pathologic conditions, this group probably contains more than one clinical entity. There were no outstanding characteristics that could be described, except that these patients were more frequently overweight than underweight and, as a rule, stronger and more active and suffered little from muscular fatigue as compared with the patients of group A. Nervousness, irritability and sensitiveness to cold were either not present or not marked. An example follows:

A. P. (figs. 3 and 4), a school girl, aged 15, came to the hospital complaining that her menstruation was delayed from one to two weeks. The only objective changes discernible were cool hands and feet, with the skin of the hands and arms slightly dry. She was of average intelligence and indulged in ordinary activities without undue fatigue. She was 10 Kg. overweight. The systolic blood pressure was 122 mm. of mercury and the diastolic pressure 74 mm. She did not appear myxedematous, although her basal metabolism dropped as low as minus 35 per cent. Desiccated thyroid in doses of 3 grains (0.19 Gm.) daily raised the metabolism from minus 26 per cent to normal without producing a significant change in her condition. A drop in metabolism occurred in conjunction with the oral administration of anterior pituitary extract in doses of 15 grains (0.97 Gm.) daily, and a restriction of diet to approximately basal requirements. There was no gross evidence of pituitary disease; that is to say, the fundi, spinal fluid and roentgenograms of the sella turcica showed no abnormalities, and the patient did not have headaches.

Another patient may be mentioned as of special interest:

C. S. (fig. 5), a schoolgirl, aged 15, first came to the clinic in November, 1928, complaining that she menstruated only every six to twelve weeks, and that she had gained 40 pounds (18.1 Kg.) in the preceding nine months. When first seen

24. As previously stated, irregularities of menstruation were not limited to this group. Considering the 196 cases as a whole, excessive menstruation was not present in any at the time of observation. There were 2 cases in which this was the original disorder, but a dilatation and curettage in both and roentgen treatment over the pelvis in one of them were followed by scanty and delayed catamenia.

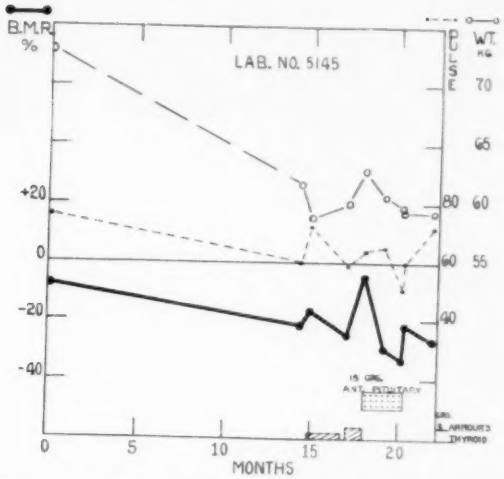

Fig. 3.—Chart showing marked depression of the basal metabolic rate in a girl, aged 15, in association with diminished catamenia and overweight, without any demonstrable underfunction of the thyroid. Three grains of desiccated thyroid daily produced no significant change except for some increase in metabolism. Loss of weight was associated with a decrease in the food intake.

Fig. 4.—Miss A. P., Dec. 20, 1928, with a basal metabolic rate of minus 16 per cent.

in the clinic her weight was 27 pounds (12.2 Kg.) above the average for her height. Her appetite was large. She had had gonorrhea about two years previously, which caused an endocervicitis. There was a tendency toward masculine distribution of hair. The shape of her hands and feet and the distribution of body fat were not typical of a true Fröhlich syndrome. There was no puffiness of her face or eyelids, although the basal metabolism for the most part varied between minus 20 and minus 25 per cent. She was unusually active and did well in school in spite of little study. Numerous social activities caused little fatigue, and she required only an ordinary amount of sleep. She was said to be precocious sexually. The administration of 6 grains (0.46 Gm.) of desiccated thyroid daily raised her basal metabolism to only minus 12 per cent and produced no clinical change. Anterior pituitary tablets were likewise without effect.

Fig. 5.—Miss C. S., Feb. 5, 1929, with a basal metabolic rate of minus 20 per cent.

In other cases we have tried an ovarian substance, corpus luteum, and anterior pituitary, singly and in combinations, as well as raising the metabolism to standard normal by giving desiccated thyroid, without material amelioration of symptoms.

It would be important to know in how many such cases, if any, the primary disorder is an underfunction of the ovaries. Active ovarian preparations have not been available long enough to determine this.

C. Hypothyroidism Without Myxedema: There were 13 patients who appeared to have an underfunction of the thyroid but no detectable edema (possibly because the condition was so mild). The essential difference between this type of patient and the others who are classed

as having no underfunction of the thyroid was the striking clinical improvement noted in the former when the metabolism was raised to standard normal by the administration of desiccated thyroid, while the latter either experienced no change or suffered from thyroid intoxication. The following case is an example of the type with mild hypothyroidism but no myxedema:

F. S. (fig. 6), a high school senior, aged 16, was lively and vivacious up to two years before examination, when she became nervous, irritable, cried easily and experienced palpitation on exertion. Muscular fatigue, sensitiveness to cold weather and sleepiness during the day developed. Constipation was marked. Menstruation was always from two to eight weeks overdue. She perspired freely. The results of physical examination were negative except for slight pallor of the skin and the fact that she was 4 Kg. overweight. The systolic blood pressure was

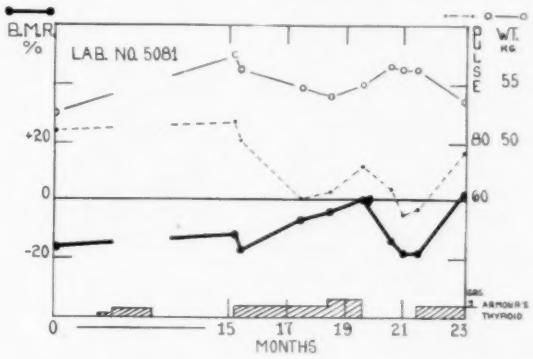

Fig. 6.—Chart showing hypothyroidism in a girl aged 16, without any detectable edema. Striking clinical improvement was noted during each administration of desiccated thyroid.

122 mm. of mercury and the diastolic pressure 94 mm. The basal metabolism ranged from minus 12 to minus 18 per cent. Desiccated thyroid in doses of 3 grains daily raised her metabolism to standard normal. She became more lively; her appetite increased; constipation and sensitiveness to cold disappeared, and her catamenia were more regular. On omitting thyroid for one month, the metabolism fell to a level of minus 18 per cent and all of her previous symptoms recurred.

D. Other Condition That Are Sometimes Associated With Low Basal Metabolism: The following cases are presented as clinical entities which have an associated low metabolism without clinical evidence of myxedema:

Malnutrition.—This case is one in which malnutrition was the associated condition.

D. C. (fig. 7), a high school girl, aged 17, entered the medical service on Jan. 3, 1927), complaining of loss of appetite, weight and strength. She had been well until nine months before admission, when, largely because of the teasing of her companions about her "corpulence" and to some extent because her appetite was failing under the emotional stress of great scholastic effort, she began to diet. She had lost 22.7 Kg. in weight (weight on admission, 31.7 Kg.), was markedly asthenic and easily irritated by noises. Amenorrhea had been present for ten months. Physical examination showed extreme emaciation, dry scaly skin, and rather abundant fine hair over the entire body. The systolic blood pressure was 78 mm. of mercury and diastolic pressure 62 mm. The basal metabolism was minus 46 and minus 48 per cent on two occasions. At no time was she considered to be myxedematous. Through psychoanalysis and a gradually increasing diet, she improved, gained 10.8 Kg. and the basal

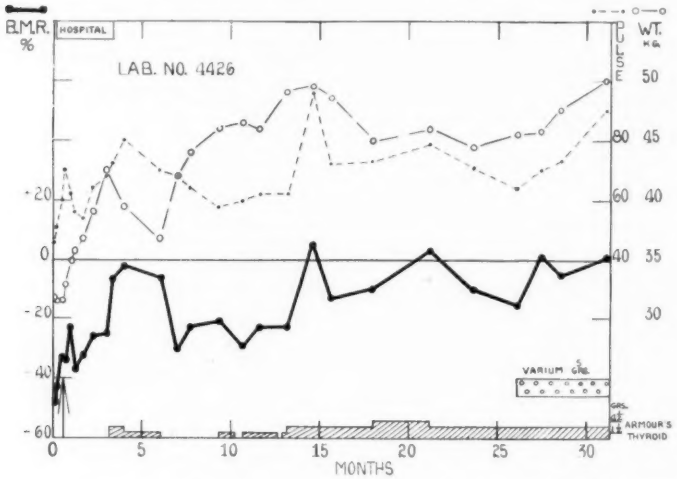

Fig. 7.—Chart showing the course of the weight and basal metabolic rate in a girl aged 17 during recovery from malnutrition.

metabolism rose to minus 25 per cent during the first three months of treatment. Desiccated thyroid in doses of 1½ to 3 grains (0.097 to 0.195 Gm.) daily was then given and raised the metabolism still further to minus 2 per cent. On omitting thyroid, the metabolism fell to minus 30 per cent. While taking thyroid she seemed to be more lively, the skin became soft and warm, and the distribution of hair returned to normal, but the opposite changes did not occur when she omitted it. Up to the present time, i. e., thirty-two months after starting treatment, her menstruation has not returned. Whether the low metabolism that persisted after the gain in weight was caused by an underfunction of the thyroid or not, is uncertain. In any case, when her metabolism was raised to normal by thyroid she was by no means completely well, and still suffered from ease of fatigue and a poor appetite.

Suprasellar Tumor.—In this case suprasellar tumor was the associated condition.

W. N. (fig. 8), a schoolboy, aged 17, entered the surgical service on Aug. 10, 1926, with definite signs and symptoms of pituitary tumor. A two-stage operation was done. A tumor was found completely burying the optic chiasm. A portion of the tumor was excised. Previous to operation his basal metabolism was minus 24 per cent. He had three roentgen ray exposures of thirty minutes each over the right and left temporal regions (the equivalent of one mild erythema dose) in October, 1926. This was repeated in January, 1927, May, 1928, and May, 1929. In January, 1929, he was a thin, frail boy, easily fatigued, sensitive to cold, and slept most of the time. There were no signs of myxedema. Desiccated thyroid in doses of 3 grains daily raised the basal metabolism from minus 39 to minus 8 per cent and he became irritable, nervous, could not sleep, and at times was

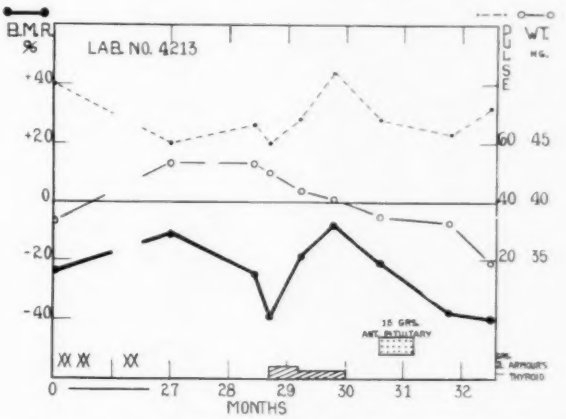

Fig. 8.—Chart of a youth, aged 19, with pituitary tumor in association with loss of weight and a well marked depression of the basal metabolism. Crosses denote roentgen treatment over the pituitary.

incontinent. On omitting thyroid, the metabolism again fell to minus 38 per cent, and he reverted to the torpid state previously noted. Anterior pituitary extract was administered orally in doses of 15 grains daily during the decrease of his basal metabolism, but was discontinued by his mother because she thought it caused increased weakness and anorexia. At the last observation in June, 1929 (three months before death), his basal metabolism was minus 40 per cent.

We have studied two other patients with suprasellar tumor, one with pinealoma, and one with cervical cord tumor, all four of whom showed low basal metabolism.

Multiple Neuritis with Muscular Atrophy.—This was the associated condition in the following case.

R. L. (lab. no. 5725), aged 19, a box toe sorter in a shoe factory, first entered the hospital in 1926 with muscular weakness and slight atrophy of the muscles of the arms, legs and abdomen, bilateral wrist and ankle drop, loss of position sense, paresthesia of the extremities and insomnia. His recovery was slow, but progressive. A diagnosis of multiple neuritis was made. He again entered the hospital on March 30, 1928, with a recurrence of all his former symptoms in more pronounced form than during the first attack. Muscular atrophy was striking and weakness was so marked that he could not walk. The basal metabolism was minus 18 and minus 21 per cent on two occasions. Again, recovery was gradual. Within six months muscle tone was regained, body weight increased 17.9 Kg. and the metabolism rose to plus 12 per cent.

Fig. 9.—Sisters, each of whom had a slight enlargement of the thyroid and a low basal metabolic rate without evidence of thyroid underfunction. On the left is Miss B. L., aged 14, with a basal metabolic rate of minus 20 per cent; on the right, Miss R. L., aged 17, with a basal metabolic rate of minus 14 per cent.

Colloid Goiter.—We have included in the miscellaneous group, 18 patients who had colloid goiter. The basal metabolisms ranged from minus 14 to minus 25 per cent. In none of them were we able to demonstrate by our criteria an underfunction of the thyroid (fig. 9). It therefore seems possible that they fall into some of the other classifications previously mentioned, in which an underfunction of the thyroid does not appear to be present.

VARIATION OF BASAL METABOLISM AND THE FACTOR OF REST

The conditions under which basal metabolism tests are done is of some importance. Except in a few instances, our subjects were outpatients. Some cases came from such a distance that two hours or more were required to reach the hospital. The effect of these rather long journeys on the basal metabolism would thus seem to be of interest.

In 20 cases (not necessarily those previously classified), observations were made on the same patient both after the usual half-hour's rest in the outpatient department and after a night's rest or longer in

TABLE 2.—*Comparison of the Basal Metabolism of the Same Person in the Outpatient Department and in the Hospital*

Patient	Laboratory Number	Average Basal Metabolic Rate in Outpatient Department, per Cent Normal	Average Basal Metabolic Rate in the Hospital, per Cent Normal	Difference, Points
Miss H. P.	5811	+ 1	−15	−16
Mrs. A. B.	4308	− 9	−22	−13
Mrs. M. O.	5013	− 8	−21	−13
Miss B. R.	4872	− 2	−15	−13
Miss D. B.	4701	− 7	−19	−12
Mr. E. T.	2259	−12	−24	−12
Miss S. H. C.	2131	− 5	−16	−11
Miss M. N.	4903	− 9	−18	− 9
Miss K. W.	5027	−10	−19	− 9
Miss M. G.	6516	−12	−21	− 9
Mr. N. P.	3142	− 8	−15	− 7
Mrs. E. McL.	4611	− 2	− 8	− 6
Miss M. V. M.	6460	−27	−32	− 5
Miss G. H.	5867	−12	−14	− 2
Miss C. S.	4133	− 8	−10	− 2
Miss J. K. A.	4664	− 8	−10	− 2
Miss M. McC.	3560	− 9	−10	− 1
Mrs. M. B.	6539	−35	−35	0
Mr. K. A.	3878	− 8	− 7	+ 1
Miss M. G.	6516	−18	− 6	+12
Average		−11	−17	− 6

the hospital. These observations are recorded in table 2. In 7 the metabolism was more than 10 per cent lower in the hospital, the maximum difference being 16 per cent. In 4 cases from fifteen months to five years elapsed from the time the determinations were made in the hospital until they were repeated in the outpatient department, thus rendering the value of the difference noted questionable. Three of these were among the 7 who showed a difference of more than 10 per cent. For all 20 cases the average basal metabolic rate in the outpatient department was minus 11 per cent, and in the hospital it was minus 17 per cent.

As previously stated, a large number of patients not included in this study had only one low rate among several normal ones. For example, one patient had 11 determinations, all of which were normal except for one of minus 17 per cent. The determination seemed to be reliable. Numerous similar situations were noted.

The data are not extensive enough to permit the drawing of definite conclusions. They do show that a patient may have a low basal metabolism in the hospital and a normal one in the outpatient department, and that in making comparisons it is desirable to have all determinations done under the same conditions. To minimize the variables affecting basal metabolism, the determination in each subject in our series was repeated until a satisfactory level was obtained.

COMMENT

In this study we have considered it our most important problem to demonstrate the presence or absence of an underfunction of the thyroid gland. The criteria that we have used may be questioned, but we know of no better than clinical improvement when the basal metabolism is raised to standard normal by administering the appropriate dose of desiccated thyroid. Failure to improve under these conditions, or the production of thyroid intoxication, together with a clinical picture in the first place that was not characteristic of hypothyroidism, certainly must at least arouse the suspicion that some other condition may exist.

While there are many exceptions, the amount of edema in hypothyroidism is roughly proportional to the depression of the basal metabolism. It might naturally be supposed that all degrees of myxedema would be encountered in association with depression of the basal metabolism, varying from slight to marked. In general however, an underfunction of the thyroid is usually marked or else is absent, and a search for cases of hypothyroidism too mild to be myxedematous is not as fruitful as one would anticipate. The fact that only 13 such cases were discovered in this study serves to emphasize its rarity.

In the past there has been a tendency to attribute all low basal metabolism to an underfunction of the thyroid, and to consider this of two kinds: (1) primary, the result of direct injury to the thyroid gland; (2) secondary, the result of loss of the stimulus to the thyroid from some other gland of internal secretion, or a result of some other pathologic condition in which the thyroid suffers with the rest of the body, e. g., malnutrition. In other words, cases similar to those that we have described have been reported as cases of "hypothyroidism without myxedema" and "secondary hypothyroidism." We feel that it has been satisfactorily demonstrated that the first condition does exist and we think that the second condition probably exists, although we have not yet succeeded in demonstrating a case. The significant thing, however, is that both conditions appear to be rare in comparison with the large

number of patients who have a depression of the basal metabolism but no thyroid underfunction.

If it is true that most of these patients have no hypothyroidism, the next problem is to discover what is the matter with them, for most of them appear to be abnormal. In this direction little progress has been made. It is possible that a careful clinical study of large groups of these patients will enable a more accurate clinical classification to be made, and perhaps furnish clues to the underlying abnormalities. It is our impression, however, that most light will be thrown on the subject as therapeutically active preparations of various glands of internal secretion become available, and the clinical syndromes associated with their absence in the body become well differentiated. For example, in a woman who is somewhat overweight and who has absent or scanty menstruation but no thyroid underfunction, it is difficult to tell whether the chief trouble is in the anterior lobe of the pituitary or in the ovary itself. The problem could soon be settled if active preparations of these organs were made. The field is comparatively large and new and will amply reward the diligent investigator. It would seem strange that with so many important glands of internal secretion in the body the thyroid should prove to be the only one that affects the consumption of oxygen.

There are, however, certain other conditions often associated with a low metabolism in which the primary fault is not underfunction of any gland of internal secretion, e. g., malnutrition (either the result of organic disease or experiment), many debilitating diseases and muscular atrophy. It can, of course, be argued that the low metabolism may result from secondary involvement of glands of internal secretion. The patient with multiple neuritis and muscular atrophy (with a metabolism of minus 22 per cent during the acute stage of his illness and a return of the metabolism to standard normal coincident with the regaining of muscle tone and recovery) is of interest. It seems highly probable that the chemical changes occurring in the large mass of muscles in the body are responsible for a considerable portion of the total metabolism. In any event, the question of the influence of muscle tone on metabolism is raised.

Low basal metabolism is not an uncommon observation in patients with colloid goiter and nontoxic adenomatous goiter. In the majority of such cases, no underfunction of the thyroid can be demonstrated, and in them it is probable that the low metabolism is caused by other factors. The mere association of a low basal metabolism with a disease is not evidence that the disease causes it, as the metabolism may have been low before its onset. In this connection a patient (lab. no. 5729) with chronic thyroiditis (Riedel's struma) is of interest. She had a right

hemithyroidectomy on April 13, 1928. The day before the operation, the basal metabolism was minus 20 per cent. The left lobe of the thyroid is still readily palpable and the same pathologic condition probably exists in it as in the other lobe. Nevertheless, her basal metabolism has been unaffected by the operation and has been repeatedly observed at a level of minus 15 to minus 21 per cent over a period of fourteen months. She is an intelligent woman, has several normal children, and for years, in addition to looking after her own home, has done dressmaking to augment the family income. Raising the basal metabolism to normal with 3 grains of desiccated thyroid daily produced no clinical change. She has no edema, her skin and hair are soft and smooth, her weight and catamenia are normal. In other words, except for the pathologic condition of the thyroid and the low basal metabolism, the woman would be considered normal. A somewhat similar case has been referred to in another study.[25]

To prove that the low metabolism was caused by the disease it must be shown either that the metabolism was normal just before the disease began, or that it returned to normal when the disease disappeared.

It is a matter of interest that most variations of the basal metabolism in the so-called normal zone of plus or minus 10 per cent are below the zero line rather than above. It is, therefore, possible that the lower limits of our standards are a little high. Du Bois[26] has recently said that the Aub-Du Bois standards are 6 per cent too high.

Perhaps three of the most outstanding facts about patients who have a basal metabolic rate of 15 to 25 per cent below the average (normal) are: (1) the large number of these persons, (2) no underfunction of the thyroid can be demonstrated in the majority of them and (3) most of them appear to be abnormal.

SUMMARY

Frequent observations have been made on 196 patients with basal metabolisms of 11 to 45 per cent below the average normal (in only 8 was it lower than minus 25 per cent), but no edema that could be detected.

At least 11 patients could be considered normal (with basal metabolic rates varying from minus 11 to minus 24 per cent), but it was often difficult to decide whether a patient was normal or abnormal.

In 13 there appeared to be an underfunction of the thyroid which was apparently too mild to result in myxedema (so-called "hypothyroidism without myxedema").

25. Thompson and Thompson (footnote 1, second reference, case 2).
26. Du Bois, E.: Communicated through Dr. Graham Lusk.

The remaining 172 patients appeared to be suffering from various pathologic conditions but not from an underfunction of the thyroid, as judged by the clinical picture and the response to doses of desiccated thyroid sufficient to maintain the basal metabolism at a standard normal level.

An exact differentiation into clinical entities is not yet possible in a large number of these cases, but a rough classification has been made, largely on the basis of symptoms.

There were 79 in whom nervousness, worry and ease of fatigue were the outstanding complaints; 21 in whom scantiness or absence of menstruation was the outstanding abnormality; and 72 who suffered from various other pathologic conditions such as starvation, pituitary tumor and muscular atrophy.

Muscle tone appears to be an important factor in regulating the rate of oxygen consumption under basal conditions.

If the basal metabolism is lower than minus 25 per cent, an underfunction of the thyroid is usually present. If the depression is less than 21 per cent below the average normal, an underfunction of the thyroid is usually not present.

Book Reviews

SOME ASPECTS OF THE CANCER PROBLEM. By W. BLAIR BELL. Price, $20. Pp. 5500. New York: William Wood & Company, 1930.

This large volume is well printed and bound and lavishly illustrated. It is in large part simply a republication of a long series of papers published by the Liverpool Cancer Research organization. These papers are connected with a series of short notes by the editor, commenting on the purpose and the value of the work.

That portion of the work which leads up to the clinical treatment for cancer is of a high scientific caliber and represents studies in all the fields of medicine which the author believed would throw light on the problem of the origin of cancer and especially those studies which lead to treatment for cancer with lead salts.

In the clinical sections, however, the reader cannot but be left unimpressed with the results obtained. The last two papers by Bell and others will be discussed briefly, the results of the clinical work being summarized. In the first of these, 227 cases were studied, of which arrest or cure of the disease was claimed in 50. A number of case histories are summarized which are illustrative of the various groups given in the author's tables, but unfortunately he does not always state which group they are made to illustrate. However, of 13 cases given which are illustrative of cures, 3 patients, numbers 178, 185 and 177, were reported as still having palpable tumors. Three others, 18, 11 and 44, underwent operations for removal of the tumors, which the author claimed were incomplete but gave no histologic proof that a tumor was left behind. In number 129 there was a carcinoma of the esophagus; no microscopic examination was made. Thus one may, by cursory examination, rule out 7 of the 13 as having no possible value as scientific evidence.

In the next paper there is a summary of all the statistics. One finds that of 566 cases, 63 were arrested or cured. Here the data presented in the illustrative case reports are still more illuminating. Four of the patients treated by lead alone, numbers 39, 22, 53 and 25, had no microscopic evidences of carcinoma. More astounding still (case 102), a patient with carcinoma of the mouth had received 80 mg. of radium for twenty-four hours as a treatment less than two weeks before the first treatment with lead was begun! Again one comes to the group of 12 patients said to have had incomplete operations. It is so well known to modern pathologists that much of the indurated area surrounding ulcerated carcinoma is inflammatory and not neoplastic that evidence of this kind must be considered totally worthless. Another large group of cases consisted of recurrences of carcinoma which had previously been confirmed by section in which no section was made to prove that the recurrent growth was carcinoma. Two patients (numbers 110 and 216) were concurrently treated by both roentgen rays and radium. In number 161 the patient presented a shadow in the lung which was diagnosed carcinoma on roentgen evidence alone. In number 365 the patient had two operations as well as lead therapy for recurrent cancer of the skin of the breast. In number 173 a gland appeared in the neck after excision of the breast after carcinoma. This gland was not examined microscopically. Also included apparently in the cures attributed to lead are 29 cases in which the patients underwent operation plus lead therapy and 10 cases in which they received lead therapy plus roentgen treatment.

This brief analysis of the statistical evidence of the therapeutic value of lead shows clearly in the reviewers mind that so far, at least, the evidence presented amounts to practically zero. In as important and difficult a field as the evaluation of any form of therapy for cancer the presentation of such slip-shod, incomplete evidence in which, in a large number of cured cases, cancer had not been proved and in a still greater number of which all the other weapons in the armamentarium of the profession had been applied, cannot be too strongly condemned.

Coupled with the fact that lead therapy for cancer has received but little consideration after attempts at its use in a large number of other clinics, one cannot help but wonder what was the reason for the republication of all of this enormous mass of material at such great expense.

SYMPTOMS OF VISCERAL DISEASE. A STUDY OF THE VEGETATIVE NERVOUS SYSTEM IN ITS RELATIONSHIP TO CLINICAL MEDICINE. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Monrovia, Calif. Fourth edition. Price, $7.50. Pp. 426, with 87 text illustrations and 10 color plates. St. Louis: C. V. Mosby Company.

The author of this work is a skilled clinician who has made a life-long study of the symptoms of disease and who consequently has been led into the maize of problems associated with visceral neurology. His clinical observations have been carefully and accurately made and are well presented. Visceral neurology is clearly described anatomically and is thoroughly considered from the physiologic and pharmacologic standpoints.

The introductory chapter consists of a plea for the general consideration of the diseased patient, the fact being emphasized that "there is not only a disease which has the patient but a patient who has the disease."

Part I begins with a discussion of the control of protoplasmic activities, and of the rôle of chemical, psychic, reflex and endocrine factors, and proceeds to a careful description of the anatomy of the vegetative nervous system. Its physiology is considered as is its pharmacology, the latter including the tests for sympathicotonia and parasympathicotonia. A chapter on the relationship of the ionic content and physical state of the cell to cell activity and nerve stimulation concludes this section.

In the second part of the book, the symptoms of disease are classified as those attributable to toxemia, those attributable to reflex causes and those attributable to the disease process itself. These are then discussed, the major part of the section being devoted to the symptoms of reflex origin and to their mode of production.

Part III describes the innervation of the important viscera with a clinical study of the more important viscerogenic reflexes. This detailed analysis, comprising almost half the book, begins with the esophagus, considers the abdominal viscera in turn and then considers the thoracic viscera, the blood vessels, the salivary glands, the pharynx, the larynx and the eye, the urogenital tract, the skin and, finally, the endocrine glands.

The correlation of symptoms with the known facts of visceral neurology is the especial task undertaken by the author. In part, the conclusions seem well proved; in part, they seem highly speculative, but in any event they are interesting. The book could be condensed a great deal by the elimination of needless repetition.

SINDROME DE OCLUSION CORONARIA. By ANTONIO BATTRO. Pp. 200. Buenos Aires: Elateneo libreria cientifica y literaria, 1930.

While containing comparatively little original matter, this monograph of 200 pages is an excellent summary of the knowledge of coronary diseases. In the first section, the anatomy of the coronary vessels is carefully worked out and contains numerous good illustrations in color as well as roentgenograms of injected specimens of human hearts. The lack of overlap of the coronary fields is emphasized in the following chapter on the physiology of the coronary circulation and one describing the clinical symptoms of infarction of the myocardium. The best part of the work consists of a series of experimental studies, giving electrocardiograms of the cases in which the coronary vessels were ligated experimentally in various places. These are backed up by microscopic sections of the same material. The author continues with case reports, showing postmortem appearances together with the electrocardiographic tracings before death of a number of both acute and chronic cases. The work is well done and clearly written and contains an extensive bibliography.

THE BASIS OF EPILEPSY. By EDWARD TRACY. Price, $2. Boston: Richard G. Badger, 1930.

The author is convinced that epilepsy is due to a disturbance of the sympathetic nervous system. The whole basis for this argument lies in the fact that spontaneously there are small white spots found on the skin of epileptic patients, which he interprets as areas of vasoconstriction. By stroking the skin with a special instrument, the white vasoconstriction line is shown to be increased in intensity in epileptic patients. This excess vasoconstriction is evidence of a sympathetic hypertonia, which is due to an imbalance of the vasomotor reflexes. This is the author's only physiologic proof. His anatomic proof consists in references to Echeverria's "Anatomical Pathologic Studies on Epileptics" of 1870, at a period when neuropathologic conceptions were in their infancy. The author attempts to diagnose incipient epilepsy by the white spots. He gives numerous case reports containing many irrelevant observations. His conclusions are, as a whole, unwarranted.

CLINICAL EXAMINATION OF THE NERVOUS SYSTEM. By G. H. MONROD-KROHN, M.D., F.R.C.P. Price, $2.50. New York: Paul B. Hoeber, Inc., 1930.

That this excellent book should have passed through five editions in the course of nine years would seem to be ample evidence of its value. It presents a careful detailed study of the examination of the entire nervous system, lucidly informing the reader how each step should be performed, the interpretation to be placed on the observations and the pit-falls to be avoided. The additions to this edition concerning ventriculography and encephalography are valuable addenda. The text is not concerned with the discussion of clinical or pathologic entities; this is a great advantage over other books on neurology as it lends to the brevity, conciseness and clearness which characterize this little volume. It should continue to find an important place among the books of the student of neurology and also the practitioner of general and specialized medicine.

LES URTICAIRES. By EDOUARD JOLTRAIN. Price, 40 francs. Pp. 417. Paris: Gaston Doin.

This small paper bound volume is devoted entirely to the clinical and theoretical study of urticaria, and therefore commends itself especially to those interested in this subject. The author, a former pupil of Widal, prefaces the work by an extensive and sympathetic biography of his teacher. The various physical and chemical causes of urticaria are considered in separate chapters. The author emphasizes urticaria caused by emotional shock and fatigue. A final chapter is devoted to the therapeutics of urticaria. A long list of general and local treatments are given, but it must be admitted that little is said concerning which of these are the treatments of choice.

Concluding this treatise is an extensive bibliography mainly referring to French literature. There are eight photographic illustrations accompanying the text.

DIE ARTEN DER SCHLAGANFALLE DES GEHIRNS UND IHRE ENTSTEHUNG. By DR. P. SCHWARTZ. Price, 48 marks. Berlin: Julius Springer.

Apoplexies are discussed under three headings: the hemorrhages associated with hypertension, the softening associated with arteriosclerosis and the embolic disorders. A thorough review of the literature is first given by the author. He then discusses the macroscopic localizations of the various types of lesions and shows how they are dependent on the blood supply of the various portions of the brain. The gross and microscopic appearances of the various lesions are described in great detail and the pathogenesis is then discussed. One hundred and fifty excellent illustrations graphically picture his work. The author has written a thorough and adequate description of the apoplexies, the numerous details of which must be studied by any one interested in the subject.

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